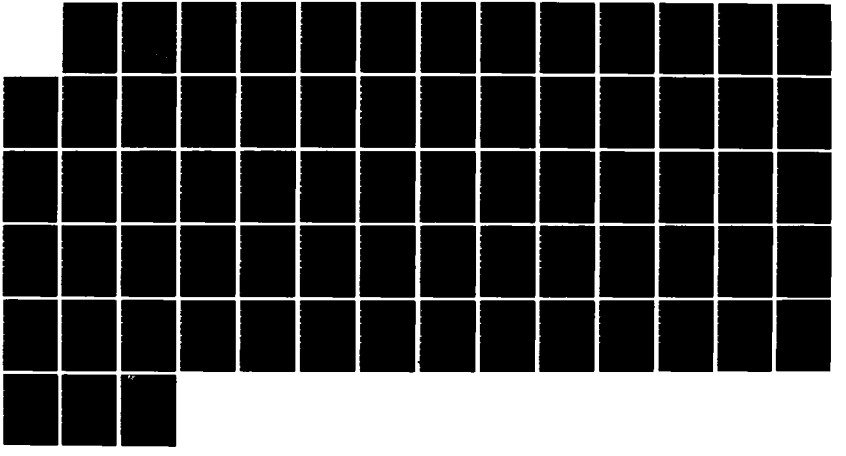
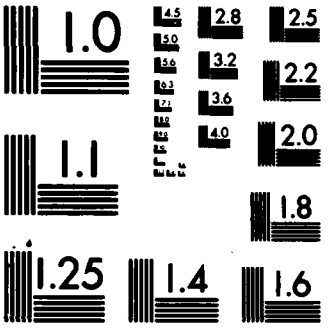
AD-A140 255 ACUTE INFECTIOUS DISEASE(U) ARMY MEDICAL RESEARCH INST 1/1
OF INFECTIOUS DISEASES FORT DETRICK MD W R BEISEL
23 MAR 84

UNCLASSIFIED F/G 6/5 NL






MICROCOPY RESOLUTION TEST CHART
NATIONAL BUREAU OF STANDARDS-1963-A

UNCLASSIFIED

SECURITY CLASSIFICATION OF THIS PAGE (When Data Entered)

# REPORT DOCUMENTATION PAGE

READ INSTRUCTIONS BEFORE COMPLETING FORM

| 1. REPORT NUMBER | 2. GOVT ACCESSION NO. | 3. RECIPIENT'S CATALOG NUMBER |
|---|---|---|
| | AD-A140255 | |

4. TITLE (and Subtitle)

Acute Infectious Disease

5. TYPE OF REPORT & PERIOD COVERED

6. PERFORMING ORG. REPORT NUMBER

7. AUTHOR(s)

William R. Beisel, M.D.

8. CONTRACT OR GRANT NUMBER(s)

9. PERFORMING ORGANIZATION NAME AND ADDRESS

U.S. Army Medical Research Institute of Infectious Diseases
Fort Detrick, Frederick, Maryland 21701

10. PROGRAM ELEMENT, PROJECT, TASK AREA & WORK UNIT NUMBERS

6.67.70.A871/BD

11. CONTROLLING OFFICE NAME AND ADDRESS

U.S. Army Medical Research and Development Command, Office of the Surgeon General
Department of the Army, Washington, D.C. 20314

12. REPORT DATE

23 March 1984

13. NUMBER OF PAGES

64

14. MONITORING AGENCY NAME & ADDRESS(if different from Controlling Office)

15. SECURITY CLASS. (of this report)

15a. DECLASSIFICATION/DOWNGRADING SCHEDULE

16. DISTRIBUTION STATEMENT (of this Report)

Approved for public release; distribution unlimited

17. DISTRIBUTION STATEMENT (of the abstract entered in Block 20, if different from Report)

18. SUPPLEMENTARY NOTES

Information regarding reprints are not available at this time.
This manuscript is an invited Chapter written for publication in a book entitled "Nutrition and Metabolism in Patient Care." Book will be edited by J. M. Kinney, K. N. Jeejeebhoy, B. L. Hill, & O. E. Owen & published by W. B. Saunders, Co., Philadelphia.

19. KEY WORDS (Continue on reverse side if necessary and identify by block number)

| | | |
|---|---|---|
| Infection | Amino Acid | Acid-base hormones |
| Nutrition | Carbohydrate | Interleukin-1 |
| Host Resistance | Fat | Fever |
| Immunity | Minerals | Anorexia |
| Protein | Vitamins | Septic shock |

20. ABSTRACT (Continue on reverse side if necessary and identify by block number)

See over

DTIC ELECTE S APR 19 1984 D E

84 04 17 023

DD FORM 1 JAN 73 1473 EDITION OF 1 NOV 65 IS OBSOLETE

UNCLASSIFIED

SECURITY CLASSIFICATION OF THIS PAGE (When Data Entered)

AD A140255 DTIC FILE COPY

The development of acute generalized infectious illnesses and serious inflammatory reactions is accompanied by the occurence of a large number of interrelated host defensive measures. These constitute the generalized acute-phase response to infection, inflammatory states, or complex trauma. These responses include the development of fever and hypermetabolism, the production of a leukocytic response, the accelerated proteolysis of skeletal muscle, the generation of free amino acids from body somatic protein catabolism, the production of a number of hormones, the synthesis by the liver of acute-phase reactant proteins and of various intracellular enzymes, the acceleration within the liver of gluconeogenesis and lipogenesis with a relative suppression of ketogenesis, the redistribution and/or sequestration of various trace elements, and, importantly, the stimulation of immune system activity. These components of the acute-phase generalized, nonspecific metabolic response to acute infection are triggered by the release from activated monocytes and tissue macrophages of endogenous mediators which are currently grouped under the term Interleukin-1.

# ACUTE INFECTIOUS DISEASE

By

William R. Beisel, M.D., F.A.C.P.

US Army Medical Research Institute of Infectious Diseases

Fort Detrick, Frederick, Maryland 21701

An Invited Chapter for the book entitled

NUTRITION AND METABOLISM IN PATIENT CARE

Edited by

John M. Kinney, M.D.,

K. N. Jeejeebhoy, M.B, B.S,

Graham L. Hill, M.D.,

and

Oliver E. Owen, M.D.

To be published by

W. B. Saunders Company, Philadelphia

The views of the author do not purport to reflect the positions of the Department of the Army or the Department of Defense.

23 March 1984

**Approved for public release; distribution unlimited**

# ACUTE INFECTIOUS DISEASE

By

William R. Beisel, M.D., F.A.C.P.

US Army Medical Research Institute of Infectious Diseases

Fort Detrick, Frederick, Maryland 21701

An Invited Chapter for the book entitled

NUTRITION AND METABOLISM IN PATIENT CARE

Edited by

Accession For
NTIS GRA&I
DTIC TAB
Unannounced
Justification
By
Distribution/
Availability Codes
Dist | Avail and/or Special
A-1

DTIC COPY INSPECTED 2

John M. Kinney, M.D.,

K. N. Jeejeebhoy, M.B, B.S,

Graham L. Hill, M.D.,

and

Oliver E. Owen, M.D.

To be published by

W. B. Saunders Company, Philadelphia

The views of the author do not purport to reflect the positions of the Department of the Army or the Department of Defense.

PROPOSED CHAPTER FORMAT

(Not for Publication)

I. INTRODUCTION

A. Concepts of Infection-Induced Effects on Nutrition

B. Concepts of Nutritional Effects on Host Resistance

II. METABOLIC RESPONSES DURING ACUTE UNCOMPLICATED INFECTIONS

A. Stereotyped Patterns of Generalized Response

B. Changes in Protein, Amino Acid, and Nitrogen Metabolism

1. Protein catabolism

2. Amino acid metabolism

3. Protein synthesis

4. Nitrogen balance

C. Changes in Carbohydrate Metabolism

1. Hormonal and substrate influences

2. Glucose tolerance

D. Changes in Fat Metabolism

E. Changes in Vitamin Metabolism

F. Changes in Electrolyte Metabolism and Acid Base Balance

1. Overhydration

2. Dehydration

3. Alterations in pH

G. Changes in Mineral and Trace Element Metabolism

III. CONTROL MECHANISMS FOR THE METABOLIC RESPONSES

A. Role of the Endogenous Mediators

Infectious diseases are the most common kinds of illness to afflict mankind; on a global basis they account for more deaths each year than any other form of disease. Even the normally healthy person will experience multiple episodes of individual infections throughout a lifetime. Because of the natural defense mechanisms of the body, and, on occasion, the added assistance of antimicrobial therapy, the normally healthy person will usually be able to control most different kinds of infecting microorganisms and recover fully from infectious illnesses after only a brief period of incapacitation.

Having a multiplicity of innate resistance mechanisms and the capacity to develop specific immunity against previously experienced antigens, normal persons are able to prevent or eliminate an invasion by microorganism species that are typically present in the usual body flora and surrounding environment, and to do so without experiencing overt disease. The human host is rarely ever free of small localized inflammatory lesions on the skin and mucous membrane surfaces, but these seldom lead to a generalized illness. However, microorganisms with high degrees of virulence, or those which penetrate anatomical barriers in unusually large numbers, can overcome the initial resistance mechanisms of the normal person to initiate an acute infectious process, with/or without clinical disease. These infections are usually followed by a full recovery, but they may become subacute or chronic, or if sufficiently severe, they may overwhem host defenses and progress to a fatal outcome.

Any process that serves to eliminate or weaken one or more of the normal host resistance mechanisms will increase the opportunity for an invading infectious microorganism to produce clinical disease.[1] Congenital

deficiencies involving a nonspecific (or generalized) host defensive mechanism or an immune system component, traumatic processes that penetrate normal anatomical barriers and allow microorganisms to enter the tissues, the presence of foreign bodies, or the development of diverse disease processes or malignancies can all increase the opportunities for an infectious microorganism to produce disease.[1,2]

On a worldwide basis, the malnutrition associated with poverty and famine is a highly important cause of depressed host resistance and this can lead, in turn, to life threatening serious infections. Furthermore, severe disease processes such as malignancy, trauma, cardiac decompensation, and pulmonary, hepatic, or renal dysfunction can each lead to a malnourished state that weakens host resistance mechanisms and predisposes the patient to an invasion by microorganisms. Such superimposed infections are often caused by opportunistic organisms that lack the virulence factors necessary to produce disease in a healthy person.

Host nutrition and infectious illnesses are therefore closely interrelated. These interrelationships can best be understood by learning how an infectious processes effects the nutritional status of the host, and, conversely, how an altered nutritional state can influence host resistance or susceptibility to an infection.

## Concepts of Infection-Induced Effects on Nutrition

Acute febrile illnesses typically stimulate a broad and complex, but highly predictable, array of metabolic and physiologic responses.[3,4] These predictable responses are considered to be "generalized" or "nonspecific" because they are similar and consistent despite the nature of the infectious

agent or inflammatory response that causes them.[5] These generalized acute-phase responses appear to be purposeful, in that they are initiated by endogenous control mechanisms. These responses apparently serve to enhance all nonspecific and antigen-specific defensive mechanisms that help to eliminate invading microorganisms and repair residual damage.[1,2] The metabolic and physiologic responses to a generalized infection induce nutritional losses from body stores. These losses generally reflect the severity and duration of an illness.[3,4] Losses of body nutrients are also influenced by the age, sex, and previous nutritional status of the patient, and by the presence of any underlying medical or surgical problems. Infection-induced nutritional losses are influenced by a complex array of biochemical, metabolic and endocrine responses and by the release of endogenous mediators from certain specialized body cells.[6,7] These responses are related to the progression and regression of the infectious process itself.[3] The sequential patterns of these metabolic and physiologic responses develop and then regress in a relatively orderly and predictable manner. Infections that becomes localized cause additional forms of nutrient loss.

Metabolic and physiologic reactions during a generalized acute-phase response to an infectious illness are closely coordinated.[1,6] The acute-phase response is characterized by the generation of fever and hypermetabolism, the production of leukocytic and inflammatory actions, and the secretion of hormones and endogenous mediators. Also, skeletal muscle protein undergoes rapid catabolism in order that amino acids already present within the body can be redistributed and used to manufacture additional glucose and a variety of unique proteins. Other changes in the metabolism of nitrogen, carbohydrates, lipids, minerals, and vitamins are included in the generalized acute-phase response to infection.

Localized infections can also result in metabolic and nutritional derangements that may be superimposed on the responses due to the generalized forms of infection. However, the consequences of a localized infection, such as diarrhea, may cause the nutritional losses to exceed (both in speed and magnitude) the losses of a generalized infection that does not produce diarrhea.

Nutritional losses incurred during an infectious illness can not be sustained indefinitely. When the supplies of readily mobilized nutritional substrates such as the amino acids become exhausted, the resultant deficiencies can seriously weaken the abililty of the body to defend itself against a subsequent or intercurrent infection, or to repair infection-induced damages in various organs and tissues.[2-4] Thus, there is a tendency for the sequence of infection and malnutrition to develop into a synergistic cycle, with each new infection causing more profound nutritional losses. Such a vicious cycle, or downhill spiral, is seen most often in the young children of underdeveloped nations, but it is also a common consequence of serious medical or surgical illnesses or trauma. Unless nutritional support is provided as an intrical part of therapy for patients with severe disease with septic complications, life-threatening nutritional deficits can occur, even in the most modern of medical treatment centers.

Generalized infectious illnesses are thus typified by a concomitant acceleration of both anabolic and catabolic phenomena.[3] During the hypermetabolic state which characterizes febrile infections, glycogen stores, fat depots, new event sized glucose, and skeletal muscle protein are utilized or consumed in excess amounts through physiologically controlled, apparently purposeful molecular mechanisms.[8] This process has colorfully been

termed "septic autocanabalism."[9] These catabolic mechanisms serve to generate endogenous nutrient substrates from stores already present within the body. This process is used to provide metabolic energy and substrate molecules which help activate and sustain a variety of host defensive mechanisms used to control or terminate the infection. Although these complex anabolic and catabolic responses occur in generalized infections of all varieties, and although these responses appear to have ultimate benefit for host survival, the catabolic phenomena are not without their nutritional costs.[4]

All host defensive systems are dependent upon anabolic phenomena that lead to the production of new protein molecules.[1] Creation of many varieties of highly specialized proteins would thus appear to be one of the major purposes of the generalized acute-phase metabolic response during an infectious process.[10] New proteins must be synthesized during the creation of additional phagocytic cells, fibroblasts, clones of specialized lymphocytes, and antigen-specific plasma cells needed for the production of immunoglobulins. Hepatic cells must produce various "acute-phase" proteins for secretion into plasma, as well as additional enzymes and metallothioneins for their own intracellular use. Protein and peptide hormones are synthesized by endocrine glands.[11] Lymphokines, monokines, lysozyme and interferons are also produced by various body cells in direct support of host defensive mechanisms.[12] The body seems willing to sacrifice components of its nonessential tissues in order to achieve these objectives. However, if these endogenous supplies of free amino acids and other nutrients become exhausted and cannot be resupplied, the continued presence of an infectious process may then lead to widespread functional failure of many intracellular processes, and, ultimately, to the failure of multiple organs, and to death of the host.[9]

Concepts of Nutritional Effects on Host Resistance

The nutritional status of a patient, both before, during, and after an infectious illness, can influence the adequacy of general host resistance mechanisms as well as immune system competence.[1,2,13] The immune system provides the body with a capacity to respond to specific foreign antigens. The immune system is enormously complex and highly integrated, with regulatory checks and balances that control each response. The immune system, with all its components, is rapidly responsive, continually vigilant, and highly precise in its ability to recognize and detect foreign antigens. Intercellular mechanisms serve to amplify the immunological response to foreign antigens, and to provide a superb capacity for "memory," by quickly responding to previously encountered antigens.

Generalized non-immunological aspects of host defense are comprised of native, natural or antigen-nonspecific resistance mechanism. Like the immune system, these nonspecific mechanisms have cellular, humoral and secretory components. These defenses are considered nonspecific because they respond similarly to a wide variety of different diseases, inflammatory or traumatic processes.[1] Lymphoid tissues of the immune system, macrophages, and other nonspecific host defensive cells have an ability to influence each other. These cells accomplish this communication by the production and release of various enzymes, biologically active molecules, and endogenous mediators. They also produce substances that can react directly or indirectly, and in a synergystic manner, to reduce or prevent the growth of invading microorganisms.[10,12]

Infectious or parasitic organisms initiate bi-directional interactions with the defensive mechanisms of the host, both immunological and

nonspecific. The influences of nutritional status on these defensive mechanisms and on microorganisms survival are also complex.[1] In most bacterial diseases, serious malnutrition is detrimental to survival.[1] Some viral diseases, however, may not progress as rapidly, or become as severe, in a person who is severely malnourished. This curious phenomenon results from the necessity of viruses to utilize the molecular mechanisms of host cells in order to replicate. Viral growth may thus be reduced if the host is suffering from nutrient deprivations that impair cellular metabolic processes [2]

## METABOLIC RESPONSES DURING ACUTE UNCOMPLICATED INFECTIONS

When pathogenic microorganisms penetrate body defenses to begin an infectious process, the first interactions are with individual body cells. These initial interactions are dependent in large measure upon the species of invading organisms and the kind of body cells that responds to the invaders.[1] Microorganisms that usually replicate in extracellular locations are handled by cells with phagocytic capabilities, such as neutrophils, blood monocytes, and tissue macrophages. On the other hand, viruses and obligate intracellular bacteria or parasites must enter some specific type of host cell (such as a hepatocyte, lymphocyte, or nerve cell) to begin their multiplication.

Metabolic changes begin to occur almost immediately in a host cell that interacts with an invading organism. This interaction can involve a burst of cellular respiration when phagocytosis is initiated, the consumption of nutrients by obligate intracellular bacteria and parasites, or in cells invaded by a virus, the takeover and control of molecular pathways within host cells by enzymes released by the virus. A phagocytic event is generally

followed by phagosome formation, an activation of cationic proteins, proteases, hydrolases, lysozyme, and myeloperoxidases, and ultimately by the generation of superoxide, singlet oxygen, and other reactive oxygen radicals.[3]

During the initial phases of an infection, i.e., the incubation period, metabolic responses are largely confined to the cells that are interacting with the invading organisms. Detectable changes in body-wide metabolic processes are initially quite subtle. However, with the appearance of generalized symptoms and fever, widespread changes in body metabolism begin to appear.[1] These changes are easily measured and, in combination, they constitute the metabolic acute-phase responses to a generalized acute uncomplicated infection. These generalized changes are initiated by endogenous cellular products released in direct response to the invading microorganism, to toxic substances produced or released by some varieties of pathgenic microorganism, or to biologically active substances released from cells that participate in an inflammatory reaction.[6,7,10,12,14] Once an infectious process has induced a generalized symptomatic illness, metabolic responses are remarkably consistent in their characteristic patterns of multiple organ participation, and in their sequential evolution.[3,4]

Stereotypic Patterns of Generalized Response.

Generalized infectious illnesses of all varieties lead to a highly predictable series of biochemical, metabolic, and hormonal responses.[3,5] In combination with fever and anorexia, these responses lead to both the hyermetabolism and hypercatabolism that cause losses of somatic cell protein and a depletion of body nutrient stores. Negative balances with losses of nitrogen and other intracellular constituents, and a decrease in body weight,

typify the expected consequences of the generalized increase in metabolic activity during fever.[3,15]

Although nutritional depletion must be recognized as the most prominent consequence of an acute infectious illness, the sequential array of changes in body metabolism actually represents an admixture of both anabolic and catabolic components.[3] Each $^{o}C$ of fever causes basal oxygen consumption of the body to increase by about 13%.[15] The resultant increase in cellular energy needs and expenditures occur at the same time that food intake is diminished by anorexia. In the face of a diminished intake of nutrients, cellular energy needs are supplied chiefly by substrates derived from sources already contained within body tissues.[15] Free amino acids, mobilized through catabolic processes in skeletal muscle and somatic proteins, are used as an important source of the extra energy needed during fever.[8,15]

Redistribution of certain trace elements accompanies the acute febrile illness and is a part of the sterotypic response to infection.[6,16] Iron and zinc are both redistributed through mechanisms which lead to their storage in the liver and other tissue.[3] Copper, on the other hand, increases in plasma because of an increased hepatic synthesis of ceruloplasmin, one of the acute phase protein reactants.[3,10]

The generalized host metabolic responses may be modified by a number of factors. These include the severity and duration of an infection or its possible progression to subacute or chronic phases, the age and sex of the patient, the presence of genetic resistance factors or partial immunity, coexisting disease or trauma, and the preexisting nutritional status of the host. Upon this generalized array of expected stereotypic metabolic changes

may be superimposed some additional metabolic consequences of the infections which become localized within certain anatomic sites or organ systems.[2,3]

The number of discrete metabolic responses during infectious illnesses is large and complex. Accordingly, responses discussed in the following paragraphs will be grouped into major categories of change, and will include those of protein, carbohydrate and fat metabolism as well as changes in vitamin, electrolyte, mineral, and trace element metabolism.

Changes in Protein, Amino Acid and Nitrogen Metabolism.

Body proteins are both synthesized and catabolized at an accelerated rate during acute febrile infections, but the varieties of proteins selected for synthesis are considerably different than those of the normal state.[10]

**PROTEIN CATABOLISM — The accelerated catabolism of skeletal muscle protein during febrile infection is stimulated by endogenously produced mediators that activate the proteolytic enzymes of muscle cells enzymes.[17-20] These mediators are now grouped under the name, Interleukin-1.[12] Although proteolysis in skeletal muscle can be quite extensive during severe illness, this process appears to be of ultimate value for host survival.[4] Skeletal muscle protein typically contains a metabolically dynamic, nutritionally balanced, labile "bank" of amino acids. With sever[illegible]a, infection or widespread inflammatory states, the labile sources o[illegible]is in skeletal muscle protein can be mobilized quickly for use in meet[illegible]h high priority defensive needs of the host. Accelerated proteolysis in skeletal muscle releases free amino acids for the synthesis elsewhere of new proteins and for the generation of metabolic energy.[21,22] Proteolysis may also be accelerated in cardiac muscle.[20]**

Extracellular proteins can also be utilized, or consumed in excess, as they participate in defensive functions. The acute-phase reactants, fibronectin, fibrin and other coagulation system proteins, and components of the complement and kinin systems are catabolized in greater amounts.[10,20-28]

AMINO ACID METABOLISM -- Branched chain amino acids released during proteolysis can be metabolized within the muscle cells as immediate sources of energy.[22] The direct cellular oxidation of branched chain amino acids also serves to generate amino nitrogen groups which can subsequently be joined to pyruvate or other carbon sources via the action of aminotransferase enzymes. This molecular mechanism leads to the de novo synthesis of alanine and glutamine within muscle cells.[22] As a result, the intracellular amino acid composition of muscle is markedly altered during sepsis.[29] Further, the free amino acids which emerge from muscle tissue during early infection-induced catabolism do not coincide exactly with the amino acid composition of normal skeletal muscle protein. Due to the sequential metabolic destruction of branched chain amino acids (leucine, valine, and isoleucine) and the synthesis of alanine and glutamine in muscle cells, the percentage of free amino acids entering the plasma is relatively low in branched chain group members but is increased in both alanine and glutamine.[22]

Because of the accelerated release of amino acids derived from skeletal muscle protein, plasma concentrations might be expected to increase. On the other hand, the anorexia-induced decline in dietary proteins and amino acids during infection along with a diminished intestinal capacity to absorb nutrients, would tend to diminish free amino acids concentrations in plasma. Another phenomena which influences these concentrations is the accelerated uptake of free amino acids by cells of the liver and other tissues for their

use in protein synthesis or gluconeogenesis. The same endogenous Interleukin-1 mediator that stimulates the accelerated proteolysis in skeletal muscle also stimulates the accelerated uptake of free amino acids by the liver.[6,7] As a result, the ultimate concentration of each free amino acid in plasma, during each stage of the infectious process, is dependent upon the divergent forces that control the rates of input or removal from the plasma pool. In overwhelming sepsis, plasma free amino acid patterns become severely deranged.[30,31]

Amino acids contribute an important substrate for the accelerated gluconeogenesis that takes place in the liver during acute infection.[22] During this accelerated gluconeogenesis, the nitrogenous component of alanine contributes an important substrate for an accelerated hepatic synthesis of urea.[8] Amino nitrogen, generated during transamination reactions associated with the increased utilization of amino acids for gluconeogenesis, is metabolized to produce urea. This process accounts for almost all of the infection-related increase in urea excretion.[8]

Most of the amino acids released into plasma during muscle proteolysis can be utilized either for the synthesis of new proteins or for energy production. However, only some of the tryptophan and phenylalanine released from muscle can be employed in the production of new proteins and, as a result, these two amino acids generally accumulate in excess in the plasma.[21] However, to compensate for this, the body accelerates the metabolic pathways that are normally used to degrade these two potentially toxic amino acids.

Some tryptophan can be utilized for the production of serotonin via a metabolic pathway controlled by phenylalanine hydroxylase, and some is

metabolized to indoleacetic acid by the action of tryptophan-2-monooxygenase. The largest portion of excess tryptophan, however, is metabolized via the kynurenin pathway, which is controlled by the rate limiting enzyme, tryptophan oxygenase.[21] Induction of this hepatic enzyme is stimulated during infection but its induction requires the permissive presence of cortisol. Tryptophan entering the kynurenin pathway is converted into kynurenin and/or other metabolic products. These kynurenin metabolites are then excreted via the urine as diazo reactants.[21]

Phenylalanine can normally be converted to tyrosine by the action of phenylalanine hydrolase, but during infection, the phenylalanine:tyrosine ratio in plasma generally increases. During severe sepsis, increases may also occur in the plasma values of sulfur-containing amino acids, including taurine, cystine, and methionine. Similarly, a rise in the plasma concentrations of free proline is to be expected during severe sepsis. The increase in plasma proline shows close correlations with a sepsis-induced accumulations of lactate and a decline in peripheral resistance and oxygen consumption.[32] Therefore, proline can serve as an excellent indicator of disease severity. Increased concentrations of proline in sepsis may be attributable to impaired hepatocyte capabilities and a reduced ability of Krebs cycle enzymes to function.[32]

Certain amino acids become methylated after they have first been incorporated into a body protein. When one of these proteins molecules is degraded, the methylated amino acids cannot generally be reused for the synthesis of new proteins or for other purposes, and therefore, the free methylated amino acids are typically excreted into the urine without further change.[3] Histidine, lysine, and arginine can all be methylated in this

manner. Measurements of the excretion of 3-methylhistidine can be used to obtain indirect information about the rates of catabolic degradation of proteins that contain it. Although the source of 3-methylhistidine appears to be limited to the contractile proteins, actin and myocin, increased 3-methylhistidine secretion in the urine generally parallels the losses in total body nitrogen and the overall catabolism of skeletal muscle protein.[3] Based on similar concepts, the post-transcriptional hydroxylation of proline produces hydroxyproline in collagen. An increase in plasma or urinary hydroxyproline is thus indirectly indicative of an excessive rate of degradation of connective tissue protein.[3]

PROTEIN SYNTHESIS -- Protein synthesis is essential for maintaining all body defense mechanisms. Proteins are needed for the creation of new cells that participate in killing the invading organisms, for the function of immune defenses, or for the repair of structural damage. Specific new (or additional) body proteins must be also manufactured for metabolic uses within cells that contribute to host defense, or for secretion by cells into extracellular body fluids. In infection as in health, each protein to be synthesized requires the activation of a cell nucleus genome, the transcription of its messenger RNA, the production of RNA-containing ribosomes, and the assembly of free intracellular amino acids into the nascent protein chain.[33,34] In some instances, sugars, lipid components, or trace elements must be added, and, sometimes, a precursor protein molecule may be formed that must subsequently be cleaved to a smaller size for functional activity to occur.

Protein synthsis is required for the production and function of phagocytic neutrophils, monocytes and macrophages, and various subsets of

lymphocytes. Fibroblasts must also be formed to assist in repair of damaged tissues. Cells must produce the proteins required for maintenance of their intracellular organelles, endoplasmic reticulum, and exterior cell wall structures and receptors. Protein hormones and various hormone-like proteinaceous substances such as the lymphokines, monokines and interleukins must also be synthesized during acute infections.

Hepatic cells must synthesize numerous enzymes and certain unique intracellular proteins such as metallothionine, hemosiderin, and ferritin.[3,16,21,35] A large variety of proteins must be produced during infection for secretion or release into the plasma.[10] These include the several different types of immunoglobulin, antimicrobial factors such as interferon, lyozyme, transferrin, and lactoferrin, components of the coagulation, complement, and kinin systems, fibronectin, and a variety of acute-phase reactant serum glycoproteins. These acute-phase proteins include alpha-1-acid glycoprotein, haptoglobin, ceruloplasmin, fibrinogen, various components of the complement system, and C-reactive protein.[10] Although neither the molecular nor physiologic functions of some of these individual acute-phase reactant proteins is known with certainty, as a group they appear to increase the ability of the body to remove infectious microorganisms from the circulation, to enhance immune responsiveness, and to block the effects of any harmful proteases or free hemoglobin that might gain access to the plasma.

The anabolic activity which creates these various proteins needed for host defense is overshadowed clinically by the more prominent wasting effects of illness.

NITROGEN BALANCE -- Body balances of nitrogen become negative soon after the onset of fever in most acute infections. Negative nitrogen balances are

largely due to catabolic processes and the use of amino acids for energy production during the hypermetabolic period.[3,4] Negative balances can be ascribed only in small part to anorexia and the reduction in dietary nitrogen intake during infection. This rapid loss of body nitrogen during infection contrasts with a tendency for nitrogen losses to be minimized during simple starvation. Urea is a predominant component in the loss of urinary nitrogen, but urinary losses of ammonia and other nitrogen-containing components such as creatinine, uric acid, alpha amino nitrogen, and diazo reactants are also increased.[8] During acute febrile illness, twenty or more grams of nitrogen may be lost per day.[4]

Changes in Carbohydrate Metabolism.

The production of glucose is accelerated in patients with sepsis or other forms of febrile infections.[3,8,15] The increased glucose production during surgical sepsis is so great that it may not be slowed by infusions of 5% dextrose.[36] This stimulation of gluconeogenesis is brought about by a combination of several hormones acting in concert, and also by the increased availability within the liver of the substrates necessary for enhanced gluconeogenesis.[11] Although manufacture of some glucose can also occur in the kidneys, little is known about the magnitude of renal gluconeogenesis in the infected host.

Although hyperglycemia and increased rates of gluconeogenesis typify the onset of a febrile infection, the capability of the body to sustain high glucose production cannot always be continued.[37,38] If the infectious process causes hepatocellular necrosis, or a functional failure of metabolic processes within hepatic cells, glucose production can also be diminished. Endotoxin or

other microbial products may interfer with the ability of the liver to synthesize phosphoenolpyruvate carboxykinase,[39] a cortisol-induced enzyme that is necessary for the production of glucose from three-carbon compounds.

Hypoglycemia can also result from an insufficient suppply of new substrate. This may occur in infants or aged individuals who lack a sizeable pool of "labile" nitrogen in their skeletal muscles, or hypoglycemia can be a problem in severe or protracted sepsis after the "labile" pool of endogenous body amino acids has become exhausted.[8]

HORMONAL AND SUBSTRATE INFLUENCES -- Glucagon and the catecholamines stimulate the accelerated production and release of glucose by their ability to activate hepatic adenylate cyclase. Catecholamine effects, however, are generally not prominent unless cardiovascular hypotension intervenes.[40] During most acute infections, the production of adrenal glucocorticoid steroids and growth hormone is also increased. These hormonal stimuli for glycolysis and gluconeogenesis occur in the face of modest increases in rates of secretion and plasma concentrations of insulin. This infection-stimulated secretion of insulin, at a time when dietary intake is reduced by anorexia, is a unique phenomenon, inasmuch as insulin secretion typically declines to its lowest possible physiological values during periods of starvation.[11]

The hormonal settings which stimulate gluconeogenesis are assisted by the presence within the liver of all of the usual substrates for hepatic production of glucose.[8] These include lactate, pyruvate, glycerol, alanine, and the other gluconeogenic amino acids. The increased availability of certain of these substrates can be accounted for by the increased output of alanine from skeletal muscle, and of lactate produced by heightened metabolism of body tissues. The shunting of three-carbon compounds to the liver as

lactate, pyruvate, and glycerol, and then back to the tissues as six-carbon glucose may be considered a "futile cycle," but this process does yield cellular energy substrates and permits the production of heat, as needed during fever.[3] Similarly, the synthesis of alanine in muscle, and its degradation in the liver to produce both glucose and urea, is an energy-inefficient mechanism, but it also serves to generate carbohydrate fuel during periods of fever.[8]

GLUCOSE TOLERANCE--Early in the course of febrile infections, glucose tolerance tests become abnormal. Baseline glucose concentrations also tend to be somewhat increased. The rise of blood glucose following a glucose meal, or a glucose infusion, reaches higher than normal values and the subsequent decline is slower.[3] The content of the glucose pool of the body may increase two to three times above normal in septic patients. The turnover and oxidation rates for glucose may also double, as may the rates of conversion of alanine to glucose.[36] Because these infection-induced increases in blood glucose values occur in the face of somewhat higher than normal plasma insulin values, some degree of cellular insulin resistance seems likely. This could be due to alterations in the number, or affinity, of insulin receptors on body cell surfaces, but information regarding this possiblity has yet to be clarified.[11]

Changes in Fat Metabolism.

Although body lipid metabolism does not exhibit changes as dramatic as those of protein or fat, endogenous fat stores of the body continue to provide a major source of necessary calories during acute infectious diseases.[41,42] Like stores of other nutrients, these lipid depots can also become depleted if

an illness progresses to a prolonged chronic state. Because of sustained or high plasma insulin values, the release of free fatty acids from triglyceride stores may be partially inhibited during acute infections, although this action may be overcome by a high catecholamine output during sepsis.[41]. On the other hand, the production of fatty acids and triglycerides by the liver is enhanced. In fact, if exogenous carbohydrate is administered in amounts too large to permit their concombitant oxidation by a febrile patient, the excess carbohydrate will be used for lipogenesis, as in periods of health. In some bacterial infections, especially gram negative ones, accumulation of triglycerides in plasma may become large enough to cause the plasma to take on a characteristic milky appearance, as is typical of some hyperlipidemias.[42]

The algebraic summation of the input and removal rates for each type of plasma lipid will determine its individual concentrations. Infectious illnesses result in a wide range of plasma lipid values, with some reports describing declining lipid concentrations, while other evidence points to an increase of some lipids in plasma.[42] This diversity is especially true for cholesterol concentrations, which may increase, decrease, or remain constant; in fact, biphasic changes can occur during the course of a single infection.

The free fatty acids of plasma tend to decrease.[43] This is due, in part, to a decline in the plasma albumin that serves as their major transport protein. Free fatty acid values may also decline because of increased rates of uptake and utilization by the liver, and/or of decreased release from triglyceride stores. On the other hand, two to three fold increases in rates of glycerol turnover in septic patients would suggest an increased release of free fatty acids from stored triglycerides. This may occur with no increase in plasma glycerol[41] which can be used rapidly for gluconeogenesis.

Additionally, the uptake and utilization of free fatty acids by skeletal muscle and the myocardium may be diminished in gram negative sepsis or endotoxemia.[22]

During infection, the hepatic synthesis of new fatty acids from the two-carbon units of acetate appears to be accelerated. At the same time, the liver may accelerate its uptake of free fatty acids from the plasma.[42] Triglycerides, as well as their lipoprotein carriers, are also produced at an accelerated rate by the liver.[42] The lipoproteins serve to transport triglycerides and other lipid moieties into the plasma. Typically, however, the liver accumulates an excess of triglycerides during periods of infection, and these triglycerides may coalesce to form numerous lipid droplets in the hepatocytes, thus creating a histologic appearance of fatty metamorphosis of liver.

Short and medium chain length fatty acids are readily transported into hepatic cell mitochondria during infection, but the transport of longer chain fatty acids into the mitochondria may be impaired. However, carnitine which contributes to the mitochondrial uptake of fatty acids, does not appear to be in short supply. The degradation of fatty acids to two-carbon units within the mitochondria appears to proceed normally, but the subsequent synthesis of ketone bodies may be inhibited, at least in part.[43] Although some ketogenesis may continue, the overall amounts of ketone bodies that are formed by the mitochondria during infection appear to be much lower than the amounts typically produced by a patient with degrees and durations of starvation similar to those seen in infected patients.[22,43] The heightened secretion of insulin during infection has been postulated as the cause for both the accelerated synthesis of fatty acids by the liver, as well as for the apparent inhibition of ketone body production.[43]

Although hypertriglyceridemia can be explained, in part, by the increased hepatic production of triglycerides and lipoproteins, there may be some slowing of triglyceride uptake by peripheral fat cells during infection. This is due to a decrease in the activity of peripheral, heparin-sensitive lipases that assist in the clearance of triglycerides from plasma.[44]

Changes in Vitamin Metabolism.

Relatively little is known about alterations in vitamin metabolism during infectious illness, although it is the general concensus that vitamins are utilized in greater amounts than normal, and that body vitamin stores become depleted.[3] Acute infections have been followed, in some instances, by the onset of classic vitamin A deficiency states, or by beriberi, pellegra, or scurvy.[45] Such complications of infection generally are seen only in persons whose anticedent nutritional state was poor. Blood concentrations of vitamin A, vitamin C, and pyridoxine may decline during acute bacterial and viral illnesses, malaria, and chronic tuberculosis.[3] Depressed vitamin concentrations have also been found to occur in the blood and tissues of laboratory animals with experimental infections. Riboflavin excretion generally increases in urine in parallel with losses of body nitrogen.[3]

Their can be no doubt that an adequate availability of vitamins is necessary to permit the full maintenance of functionally adaequate host defenses.[13] The adrenal cortex normally contains large amounts of vitamin C and these stores become depleted during active steroidogenesis.[11] Neutrophils also contain large amounts of vitamin C, and these stores are also depleted during phagocytosis. The group B vitamins, vitamin C, and folic acid all contribute to the adequacy of phagocytic activity by host cells.[1,13] A number

of vitamins, including A, riboflavin, nicotinamide, pyridoxine, $B_{12}$, vitamin E, and folate all appear to contribute to the immune functions of B- and T-lymphocytes, as well as to macrophage activities.[13] The antioxidant activity of vitamin E may help to protect cellular lysosomes, as reported in leprosy.[1] Parasitic infestations of the gut, especially those involving tapeworms, may divert intestinal vitamins to the parasites and thereby reduce the amounts absorbed for use by the host.[1,3]

Some antimicrobial drugs can influence vitamin metabolism. Pyridoxine depletion has been noted in patients receiving isoniazid. On the other hand, patients with tuberculosis may become overly sensitive to vitamin D and may then develop hypercalcemia.[3]

Changes in Electrolyte Metabolism and Acid-Base Regulation.

Fluid and electrolyte balance metabolism problems can have a profound effect on the outcome of infectious illnesses. The body tends to retain an excess of both extracellular salt and water unless severe or protracted vomiting and diarrhea are component parts of the infection and cause undue losses of intestinal and gastric fluids.[3]

OVERHYDRATION — In typical infections, an increased secretion of aldosterone causes salt to be retained by the kidneys.[11] An excess of body water may also be retained. In some diseases, such as Rocky Mountain spotted fever, the hemorrhagic fevers, and infections which localize within the cranial vault, an exaggerated secretion of antidiuretic hormone from the posterior pituitary gland may occur in a physiologically inappropriate manner.[11] Overproduction of antidiuretic hormone causes body water to be retained in excess, thereby initiating a dilutional hyponatremia with the possibility of a life threatening fluid overload.

DEHYDRATION -- On the other hand, protracted diarrhea causes isoosmotic losses of intestinal electrolytes and fluids. In high volume diarrheas such as occur in Asiatic cholera or E. coli enterotoxemia, the principal losses of intestinal electrolytes occur as sodium, potassium, and bicarbonate.[46] With lower volume diarrheic losses of body fluids, or with chronic diarrheas, the loss of body potassium is greater than that of sodium, and only little bicarbonate is lost. Conversely, with vomiting, there is a loss of gastric hydrochloric acid. These isoosmotic losses via the gut can result in a serious depletion of extracellular water, with concomitant hemoconcentration and acid-base imbalances.[3]

ALTERATIONS IN pH — Complications of various infectious diseases can produce every known type of derangement in acid-base balance. The onset of fever is accompanied by accelerated respiration. This tachypnia causes an exaggerated loss of carbon dioxide.[3] The respiratory alkalosis that ensues is typically seen during all early febrile infections and it persists for varying periods of time. The initial alkalosis may then be replaced by other varients of acid-base imbalance as various metabolic and physiologic responses to illness begin to evolve. If the exchange of pulmonary gases is blocked because of congestion or consolidation of alveolar spaces, as in pneumonia or other pulmonary infections, retention of carbon dioxide can then lead to respiratory acidosis.[3] Similarly, if respiratory muscle function becomes impaired by paralysis in diseases such as poliomyelitis, tetanus, or botulism, respiratory acidoses will also emerge.

As an infectious process proceeds, acid metabolites tend to accumulate. These can swing the acid-base equlibrium in the direction of metabolic

acidosis. With high fevers or septic shock, the production and accumulation of lactic acid are markedly increased. With severe sepsis, an increased shunting of pulmonary circulation blood will further reduce arterial blood oxygenation.[47,48] The metabolic acidosis due to any of these causes can seriously affect body cellular functions if an infection is severe and protracted.

The development of metabolic alkalosis is seen only rarely in an infectious disease, but it can occur during severe persistent diarrheas that deplete the body of potassium.[46]

Changes in Mineral and Trace Element Metabolism.

With the onset of symptomatic infectious illnesses, a number of changes occur in mineral and trace element metabolism. Sizable losses from the body occur of all principal intracellular elements. Such losses tend to be porportional to the concomitant losses of body nitrogen. Magnesium, potassium and phosphorus losses are of this variety, as are losses of sulfur and zinc. The loss of intracellular elements can be demonstrated *in vitro* by subjecting tissue culture cells to a chlamidial infection.[49] If the infectious illness is associated with muscle paralysis, muscle tissue losses are still greater, and a concomitant disuse atrophy of bone will cause additional losses of the principal bone minerals, calcium and phosphorus.

Unusual, but transient, changes in phosphorus excretion are associated with respiratory alkalosis. During periods of heat-induced tachypnia, inorganic phosphates may virtually disappear for a time from urine and sweat. Despite this transient retention, major losses of phosphorus eventually occur during febrile infections along with concomitant losses in

other minerals. Losses of intracellular potassium also parallel those of nitrogen in generalized infections.[3] Should diarrhea occur as a component of the illness, fecal losses of potassium and magnesium are increased disproportionately.

Although major changes in calcium balance have not been associated with infectious illnesses, other than those producing muscular paralysis, changes in calcium metabolism are undoubtedly of importance at the cellular level.[3] Because of the actions of calmodulin within cells, rates of flux of calcium across cellular membranes may be altered during acute infection. This phenomenon helps to modulate the actions of many hormones and perhaps some of the endogenous mediators.

Three of the trace elements show unique changes in their concentration in plasma during infections and other inflammatory states. These changes are due principally to a redistribution of these elements within the body. This redistribution is initiated by the actions of the endogenous mediater, Interleukin-1, which stimulates the hepatic accumulation of iron and zinc and also leads to the hepatic secretion of copper as a component of ceruloplasmin.[6,7]

Within several hours after the release of Interleukin-1 by monocytes and macrophages that are activated by phagocytosis or other stimuli, the liver begins to accumulate both iron and zinc. Although zinc cannot normally be stored in large amounts within the liver, Interleukin-1 stimulates the hepatic synthesis of intracellular metallothioneins.[35] This unique protein binds zinc and retains it within hepatocytes during the course of acute infections.[50] On the other hand, iron is sequestered through its incorporation into hemosiderin and ferritin in various tissue storage sites.[6,7,16] The zinc and iron tend to

remain in their sequestered sites throughout the duration of an active infectious process, and because of this, the availability of iron and zinc is reduced for physiologic release or utilization in other sites. A diminished intestinal absorption of iron also contributes to the hypoferremia of infection.[16]

The same mediator that stimulates the liver to sequester iron and zinc, Interleukin-1, also causes the liver to synthesize and release large quantities of the acute-phase reactant proteins, one of which is ceruloplasmin.[10] The rise in serum copper is somewhat slower than the decline in plasma iron and zinc, and copper concentrations remain elevated for a somewhat longer period after an infection has been cured. The return of plasma copper to normal baseline values is dependent upon the rather slow half-disappearance time of ceruloplasmin.

## CONTROL MECHANISM FOR THE METABOLIC RESPONSES

Virtually all normal metabolic pathways and intracellular molecular control mechanisms become involved in one or more ways in helping the body to survive an invasion by infectious microorganisms. The normal physiological control mechanisms used for adusting cellular metabolic functions continue to retain their importance in regulating many of the metabolic alterations during infectious processes. But in addition to these usual physiologic controls (that include both neuronal and hormonal components), the body possesses a normally inactive, ancillary, hormone-like control mechanism that can be brought rapidly into play whenever it is needed. This mechanism serves to initiate the generalized acute-phase metabolic responses to any acute infectious, traumatic, or pathologic process that includes, as a component, a

prominent inflammatory reaction. This standby control mechanism begins to function whenever blood monocytes or tissue macrophages are activated.[7,10,12,14] This will occur if these cells engage in phagocytosis or are stimulated by any of a variety of immunological or chemical substances. With activation, these phagocytic cells rapidly synthesize and release endogenous mediator proteins. When released into the circulation, these hormone-like mediators stimulate generalized defensive responses throughout the body. Such responses should be viewed as physiological reactions rather than as pathological events. These mediator-induced responses include the development of fever, the appearance of leukocytosis, the production of acute-phase reactants by the liver, the acceleration of skeletal muscle proteolysis, the increased flux of free amino acids into and out of the plasma pool, the redistribution of certain trace elements, the release of certain hormones, the generation of energy-yielding substrates, and, also, the activation of cells of the immunological system.[7,10,12,14] Anorexia is another prominent component of the generalized host response, but the initiating mechanism remains unidentified.

In addition to the controls exerted by neurologic stimuli, hormones, and hormone-like endogenous mediators, a number of physiologic events produce secondary influences on host metabolism. Fever has an important influence on all body cells by stimulating increased basal metabolic activity and oxygen consumption.[15] The inflammatory process in localized areas causes initial physiologic changes and metabolic alterations in local cells. These local events can progress in severity to cause single or disseminated areas of acute pathology and necrosis, or the inflammatory process can evolve into a more chronic granulomatous reaction.

Role of the Endogenous Mediators.

Endogenous mediators are released from phagocytic cells following: a) the onset of a localized inflammatory response, b) an infection by microorganisms that do not invade body cells, or c) the death of host cells caused by microorganisms that replicate in intracellular locations. Localized phagocytic cells, mast cells and other tissue cells, and the circulating leukocytes and platelets all give off biologically active substances, either as secreted products or as cellular enzymes or other constituents liberated at the time of cell necrosis. Most of these endogenous substances are locally active, but some exert their effects only after escaping from the localized area. When macrophages and monocytes become activated, they produce the highly important endogenous mediator, Interleukin-1, which has widespread functions throughout the body in stimulating or triggering various generalized acute-phase defensive measures.[6,7,10,12,14]

The mechanism for releasing Interleukin-1 represents a nonspecific type of host response, in that many different kinds of stimuli can lead to activation of the system that causes the cellular production and release of this hormone-like substance.[12] Interleukin-1 is believed to be a small protein that circulates in the form of monomers, dimers or trimers. A unifying concept[12] postulates that Interleukin-1 may act in a manner roughly parallel to the known actions of several hormones and and of some toxins which stimulate a series of distinct and successive events after attachment to cellular membrane receptors. A number of hormones have been shown to exert their initial action by binding to cell surfaces and stimulating the activity of cell membrane adenylate cyclase. When activated, this enzyme generates

intracellular cAMP. The cAMP acts as a second, intracellular messenger that directly triggers some unique function of the stimulated cell. The cellular effect produced by the hormone depends on the biologic role of the particular cell stimulated, triggered by its molecular response to cAMP. The analogous, proposed action of Interleukin-1 also involves an initial binding to the cell surface, followed by the activation of cell membrane phospholipase A2. This action of Interleukin-1 is similar to that of calcium ionophores which cause an increase in calcium uptake by the cell, thereby activating effects in various types of cells identical to those of Interleukin-1.[12] Following $Ca^{++}$ uptake and the activation of phospholipase A2, there occurs a hydrolysis of phospholipids contained in the surface membrane of the cell, and the intracellular release of arachodonic acid. Arachodonic acid is analogus to cAMP in this unifying concept in that it stimulates subsequent steps of cellular activity. Again, the subsequent steps are dependent upon the responsive molecular mechanisms characteristic of the cell itself. Cells that possess an active cyclooxygenase pathway convert arachodonic acid into one of the prostaglandins, and thereby account for certain aspects of the biological activity of Interleukin-1. On the other hand, cells that convert arachodonic acid to one of the leukotrines initiate other actions known to be stimulated by Interleukin-1.[12]

The cells possessing cyclooxygenase pathways include neurones, fibroblasts, and skeletal muscle contractile cells; in these cells, the actions of Interleukin-1 can be blocked by certain drugs such as aspirin or ibuprofen, that can inhibit the cyclooxygenase pathway.[12] In the temperature regulating center of the brain, the release of prostaglandin leads in turn to neuronal stimuli that produce fever. In skeletal muscle cells, prostaglandins

lead to the activation of cellular proteases that cause the degradation of skeletal muscle protein. In fibroblasts, the release of prostaglandin activates collagenases that contribute to the destruction of collagen in various arthritic diseases.[12]

Conceptually, the leukotrines could have the responsibility to serve as intracellular messengers for cellular actions of Interleukin-1 that are not inhibited by the cyclooxygenase blockers. Effects of Interleukin-1 not blocked by these drugs include the initiation of leukocyte production, the release of pancreatic islet hormones, and the numerous metabolic changes occurring in hepatocytes, including the accelerated uptake of amino acids, zinc and iron, and the triggering of the mechanisms for producing proteins included in the acute-phase reactant group.[12]

Interleukin-1 is now used as a single common name for several previously described substances including lymphocyte activating factor, endogenous pyrogen, leukocytic endogenous mediator, and leukocytosis promoting (or inducing) factor.[12] It is not known if all these endogenous mediators exist as a single moleculer species, or if they actually represent a family of closely related molecules. The exact structure is not known for any of the substances currently termed Interleukin-1. However, it may be concluded that Interleukin-1 is the key mediator of the generalized nonspecific acute-phase host response to microbial invasion or other inflammatory processes, that Interleukin-1 acts in a hormone-like manner during infection and inflammation, and that the biological activities of Interleukin-1 account for numerous aspects of the acute-phase reaction.[7,10,12,14]

Actions of Interleukin-1 demonstrated <u>in vitro</u> support this concept. Stimulation of hepatocytes in culture leads to a production of fibrinogen,[51]

in vivo actions on bone marrow cause colony cells cause an increase in their proliferation,[52] actions on skeletal muscle induce proteolysis,[17,18] effects on articular fibroblasts stimulate the release of collagenase,[53] and actions on the isolated pancreas result in the induction of insulin secretion.[54] Accordingly, secondary mediation of Interleukin-1 activities by the central nervous system or other hormones need not be postulated. Some stimuling effects of Interleukin-1, however, require the permissive presence of glucocorticoids.[55] These hormones must be present to allow hepatocytes to induce the production and secretion of acute-phase reactants that are not produced by the liver during normal health.[55]

It is generally believed that the major actions of Interleukin-1 are beneficial for host defenses. This mediator has been shown to appear in the plasma of patients shortly before the onset of symptomatic infectious illnesses and to persist throughout the course of illness.[56] The production of fever increases body metabolic rates, and the production of insulin leads to glucose utilization. The heightened uptake of amino acid by the liver, when combined with the accelerated proteolysis of skeletal muscle, make possible the gluconeogenic activities of the liver as well as the ability of hepatocytes to synthesize various enzymes, metallothioneins and the acute-phase reactant proteins.[3,7,10,15]

The actions of Interleukin-1 on the lymphoid systems is a stimulatory one.[12] Interleukin-1 does not cause lymphocytes to proliferate, but, rather, it directly enhances the overall activity of B-lymphocytes to express surface markers and to produce immunoglobulins.[12] It also stimulates certain T lymphocyte subsets to produce Interleukin-2, which in turn, stimulates proliferative activity. Working in concert, Interleukin-1 and Interleukin-2

thus act as an amplifying mechanism, enabling the immune system to respond more quickly and more positively to the presence of new foreign antigens.

On the other hand, not all of the actions of the Interleukin-1 mediators may be helpful to the host. By stimulating the production of collagenases by articular fibroblasts, Interleukin-1 may actually contribute to damage within joint spaces during arthritic processes.[12,54] Excessively high fevers can also be dangerous to the host, triggering convulsive seizures and other harmful effects.[15]

Role of Hormones.

A number of hormones play a role in the metabolic responses to infection, although the hormonal effects, in some instances are of limited duration and magnitude. As a rule, host resistance is optimal when endocrine functions are normal. Too much, or too little, of certain hormones tends to be detrimental.[11]

ADRENAL HORMONES -- An increased secretion of adrenal glucocorticoid hormones begins with, or shortly before, the onset of fever during most symptomatic infections.[11] However, the maximal increase in the daily rates of cortisol production during early illness generally achieves values only two to five times normal. During early illness, plasma cortisol looses its circadian periodicity and tends to maintain concentrations near, or slightly above, the plasma concentrations normally reached during peak morning hours. The increase in glucocorticoid secretion is accompanied by smaller increases in the output of adrenal ketosteroids and pregnanetriol. These ACTH-mediated adrenocortical responses do not persist beyond the onset of recovery. In fact, if an infection becomes subacute or chronic, the production and urinary

excretion of adrenal cortiosteroids and ketosteroids generally falls below normal.[11]

If an infectious illness progresses to a agonal stage or is complicated by the onset of septic shock, a functional failure of hepatic enzyme systems may lead to an inabililty of the liver to metabolize free cortisol to its water-soluble metabolites. Plasma cortisol concentrations may then increase markedly. On the other hand, if a hemorrhagic diathesis leads to adrenal gland infarction, glucocorticoid production may cease.[11]

As fever progresses, aldosterone secretion begins to increase gradually.[11] The aldosterone increase does not coincide in timing with the more rapid increases of plasma cortisol. Following cessation of fever, aldostrone secretion typically abates rather gradually, instead of sharply, as is usually seen with cortisol secretion. The heightened production of aldosterone contributes to a renal retention of salt and water during acute infectious diseases. Loss of tissue constituents or body weight during an infection may be masked somewhat by a retention of extracellular fluids. In critically ill patients with septic shock, plasma aldosterone values may fall despite the fact that renin concentrations are increased.[57]

A tendency for excessive body water to accumulate during severe infections has also been attributed to an inappropriate secretion of antidiuretic hormone. Because of fluid retention during fever, the early convalescent period is often characterized by a diuresis of excess fluids.

GLUCOREGULATORY HORMONES -- The glucoregulatory hormones are also intimately involved in host responses during febrile illnesses.[8,11,43] Fasting plasma concentrations of insulin, glucagon, cortisol, catecholomines and growth hormone all tend to be increased and the hepatic production and

release of glucose is accelerated as a consequence. The increases in plasma glucagon are considerably greater than those of insulin, so that the molar ratio to insulin to glucagon tends to decrease.[43] Insulin effectiveness in peripheral tissues also seems to be impaired during febrile illness,[11,30] suggesting that some factor in the sick patient is able to alter the cellular uptake or manner of response to elevated plasma concentrations of insulin.

The production of catecholamines may increase slightly during, and even before, the onset of symptoms in mild infections.[58,59] However, catecholamine values are markedly increased during severe infections, especially those accompanied by hypotension.[31] The tissue of patients with bacterial sepsis may not respond to the catecholamines in a fully normal manner. In any event, the net response to the effects of glucoregulatory hormones during early infection is to increase the production of glucose and the release of glucose from glycogen stores. In the event of substrate depletion or hepatocellular dysfunction, gluconeogenesis cannot be sustained and hypoglycemia may occur.

THYROID HORMONES -- Thyroid hormone responses do not appear to play a major role in influencing host metabolism during infection. Although thyroid hormone concentrations in plasma tend to decline during early stages of illness, the thyroid gland seems to respond quite slowly.[11,60] This combination of events cause a biphasic sequence of thyroid hormone concentrations in plasma. Early in infection, an accelerated disappearance of plasma T4 and T3 is typical. These changes are accompanied by reciprocal increases in reverse T3.[60] Such phenomena are due primarily to cellular effects occuring outside thyroid gland, although the binding avidity of plasma proteins for various thyroid hormones may be altered as well. These plasma

changes are indicative of an increased utilization and deiodination, plus an altered metabolism of thyroid hormones by the liver, blood leukocytes, and other peripheral tissues.[11] This decline in plasma concentrations of the thyroid hormones is not met, as would normally be expected, by an outpouring of hormones from the thyroid gland. Rather, a sluggish response by the pituitary-thyroid axis seems to allow for a depression in major thyroid hormone values during the early stages of infection. However, later during recovery, the thyroid gland output of its hormones tends to rebound, and hormonal values in plasma may actually overshoot their normal concentrations for a time.[11,60]

Role of Pathophysiologic Events.

FEVER -- fever is probably the most easily recognized clinical and physiologic component of the generalized acute-phase host response during early infection. Fever alters host metabolic functions by increasing the rates of intracellular metabolism in proportion to the amount of increase in body temperature.[3,15] Metabolic processes within cells are generally accelerated and the consumption of oxygen is also stimulated. Fever may help to amplify and accelerate some of the other metabolic effects of Interleukin-1.[12] There is evidence that the ability of lymphocytes to function and to secrete immunoglobulins is enhanced at the higher body temperatures achieved during the clinical fevers seen with most infectious illnesses.

ANOREXIA -- Anorexia also plays a role in influencing host metabolic activities by decreasing the intake of dietary nutrients.[3] This decrease in availability of new, exogenous substrates, at a time when fever is causing

body tissues to speed up their metabolism, forces the utilization of substrates that are already present in endogenous tissue stores and depots of the body. Because of fever, the metabolic responses to a diminished dietary intake due to infection-induced anorexia are considerably different than those seen when the diminution of dietary intake is due to simple starvation.[3]

With simple starvation, body-wide adaptive metabolic responses quickly become operative. These responses are directed toward a maximal conservation of the body stores of nitrogen. Thus, during simple starvation, body energy metabolism is rapidly transformed to an almost total fat-dependent economy. Free fatty acids and ketones are produced in excess and these rapidly become the major fuels used to supply cellular needs. Cells of the central nervous system rapidly induce new enzymes that allow the brain to utilize ketone bodies instead of glucose as a major source of energy. Both the production and use of glucose are then minimized, along with the need to use amino acids as substrates for energy production. These adaptations serve to conserve body nitrogen stores and to reduce the output of urinary nitrogen to minimal values, i.e., approximately two to three grams in the starving adult who is otherwise normal.[61] These starvation-induced mechanisms for nitrogen conservation are not initiated during the anorexia of acute infectious illnesses. Rather, body nitrogen stores are actively mobilized and consumed, both as an important direct energy sources and as the additional substrates needed to produce glucose for meeting the added caloric needs induced by the presence of fever.[3] At the same time, body ketone production is minimized rather than increased.[43] As a result of infection-induced metabolic responses, negative balances of nitrogen are magnified despite the presence of anorexia, rather than being reduced as in sinple starvation.

INFLAMMATION -- The development of a localized inflammatory response is attended by the usual symptoms of heat, redness, swelling and pain. These symptoms are each related to metabolic and physiologic events that take place in the localized region.[62] The initial cellular injury liberates biologically active substances that stimulate local vasodilatation, capillary wall "stickiness," and an ingress of leukocytes which amplify the local responses. The release of locally active substances include proteolytic enzymes liberated from the lysosomal contents of degraded phagocytes, histamine from mast cells, and serotonin from blood platelets. Fibrinogen deposition in and around zones of inflammation helps to limit the area of cellular damage. Fibrin deposition also helps to minimize the escape of proteolytic enzymes from the zone of inflammation. Eventually, the fibrin strands contribute to the healing process.[3]

As described in earlier paragraphs, the inflammatory process serves to activate local monocytes and macrophages, causing them to release Interleukin-1 and other monokines.

SEPTIC SHOCK — The hypotensive shock that accompanies some infections, especially gram negative ones, causes additional concomitant additional changes in body metabolism. These changes are due to the slowing and stagnation of blood flow, to red cell pooling, and ultimately to a diminished delivery of oxygen to peripheral vascular beds.[31,37,47,48,63-65] The resultant pathological conditions are accompanied by an exaggerated production of lactic acid and other acidic metabolic wastes. Under these circumstances, individual cells of various organs and tissues cannot maintain their normal metabolic capacity to perform biochemical and physiological functions. With the metabolic failure of individual cells, functional failure of single or

multiple organs will follow. All of these phenomena represent pathological changes that are superimposed upon, but are not a part of, the generalized early metabolic and physiologic responses to an infectious illness.

LOCALIZED INFECTIONS — The localization of an infectious process within a single organ system can also disrupt the function of individual cells and the organ itself. The metabolic consequences different from, but may be superimposed upon, the generalized acute-phase metabolic responses to an infectious process. Hepatitis viruses or other viruses with hepatic trophism can directly affect the function of individual liver cells and lead to death of hepatocytes. Such a viral localization can seriously impair hepatic function for varying periods of time. Since the liver plays a highly important role in support of the generalized acute-phase metabolic responses to infection, loss of hepatic functions can have serious consequences.[37] The most important of these involve the inability to produce and secrete bile acids, to manufacture glucose, and to degrade or metabolize potentially toxic substances. Dangerous hypoglycemia is of possible clinical importance in severe hepatitis. Failure to metabolize free amino acids in a normal manner may be expected to lead to hepatic encephalolapthy, as manifested by characteristic neuromuscular contractions and eventually by coma. During the course of acute viral hepatis, generally in the second week, the sequestration of iron within the liver can no longer be maintained, and hyperferremia can result.[3] Disturbances in the binding of zinc to its plasma carrier molecules (proteins and certain amino acids) has also been described during acute viral hepatitis.[3]

Similarly, acute nephritis can lead to physiological disruptions of kidney function and to the changes in body metabolism typically associated

with renal failure and uremia. As previously mentioned, severe pulmonary consolidation or respiratory muscle paralysis can lead to an impaired exchange of respiratory gases, anoxia, and derangements in acid base metabolism. Myocarditis or pericarditis can produce cardiovascular system dysfuction. In addition, infections that become localized within the cranial vault can often stimulate an inappropriate secretion of antidiuretic hormone, followed by an abnormal accumulation of total body water, and the possibility of a cardiovascular system fluid overload.[3,11]

## NUTRITIONAL CONSEQUENCES OF ACUTE INFECTIOUS ILLNESS

All symptomatic acute infectious illnesses generate biochemical and metabolic responses that influence the nutritional status of the host. The major nutritional consequences are the result of a depletion of body nitrogen and the loss of elements that are normally found in intracellular locations.[3] Losses of bony minerals and extracellular electrolytes can also occur under circumstances described in previous paragraphs. In addition, most generalized infections cause some loss of vitamin stores, although infection-induced vitamin depletion seldom becomes clinically overt in patients seen in the "developed" nations.

The magnitude of these individual nutrient losses is dependent on several factors, including the severity of illness, the magnitude of fever, and the duration of illness.[3] These factors, in turn, may hinge upon the pre-illness presence of any cellular or humoral immunity that can provide some degree of protection from the invading microorganism. Nutritional losses will also be influenced by the anticedent nutritional status of the patient at the time the infectious process begins. Chronic severe infections, such as tuberculosis, can markedly deplete the body of its nutritional stores and lead to a

dangerous state of cachexia. On the other hand, parasitic infestations that establish a chronic symbiotic relationship with the host may have little apparent effect on nutritional status.

## Depletion of Stored Body Nutrients

A depletion of the nutrients contained in, or stored within body tissues does not generally begin during an infectious process until after the onset of symptoms and fever. Metabolic changes within single cells during the period of an incubating illness are generally too subtle to cause a measurable nutritional depletion, although biochemical values in plasma or tissues may be influenced.[3]

NITROGEN LOSSES -- With the onset of fever, the combination of anorexia and the enhanced production of glucose from amino acid substrates leads to the hepatic synthesis of urea.[8] Urinary losses of urea plus those of other nitrogenous compounds such as creatinine, uric acid, alpha amino nitrogen and the diazo reactants, in combination with varying degrees of anorexia, produce sizeable losses of body nitrogen.[3] Added nitrogen can be lost directly through sweat or exudates, or via a loss of blood, if hemorrhage is a part of the infectious process. Sources of amino acids that constitute the so called "labile nitrogen" pool within the body are located chiefly in skeletal muscle and other somatic tissues. Since these pools are finite, and of relatively limited size (even in a normal healthy adult male), they can become severely depleted by a week-long period of illness.[3,9] Rates of nitrogen loss are usually greatest during the first few days of fever. Thereafter, the daily losses of body nitrogen begin to taper off gradually even though fever persists.[3,4] After a febrile period of two to three weeks, continued losses

of nitrogen become almost negligible, and the body re-establishes a new equilibrium in nitrogen balance despite the fact that the infectious process is still active. This new equilibrium, however, is generally re-established only when the body is markedly cachetic.[3,4]

LOSS OF INTRACELLULAR NUTRIENTS -- Body stores of the intracellular elements tend to be lost in relative proportion to the rates of nitrogen loss and to the normal ratio of nitrogen to each element present in skeletal muscle tissue. Elements generally lost in proportion to the losses of nitrogen include magnesium, potassium, phosphorus, zinc, and sulfur.[3] Phosphorus losses, however, may be initially minimized by the disappearance of inorganic phosphates from the urine and sweat during the period when respiratory alkalosis and hyperventilation are taking place. On the other hand, losses of phosphate may be increased if there is body immobilization (through paralysis or other factors of illness) sufficient to produce a disuse atrophy of bone. In such instances, excess bone mineral components such as calcium and phosphorus will be lost proportionately.[3] No evidence is available concerning a total-body depletion of other trace elements during infection.

Under normal conditions of health, carbohydrate stores of glycogen in tissues are quite small, but they can be used to supplement ongoing gluconeogenesis as may be required to meet cellular needs for carbohydrate fuels.[8] An infection places special demands on body systems for generating carbohydrate fuels, but these demands can generally be met as long as cellular gluconeogenic mechanisms remain functional and an adequate supply of gluconeogenic substrates can be supplied.[15] In severe or protracted infections, especially those associated with sepsis caused by endotoxin-containing bacteria or those associated with hepatocellular

dysfunction, hypoglycemia and a depletion of cellular glycogen stores may be expected.[37,64] Little is known about how body cells provide (or fail to provide) carbohydrate components for the glycoproteins produced during periods of infection.

Body lipid stores are rarely depleted during the initial phases of an acute infectious illness. However, if the illness becomes subacute or chronic, fat stores will gradually be utilized to supply metabolizable free fatty acid substrates, and eventually body fat depots will become depleted.

Adequate data are not available to demonstrate chronic or measurable losses of most body vitamins. In contrast, an increase in urinary riboflavin may occur in parallel with the increased loss of body nitrogen.[3] Any depletion of body stores of other vitamins must be estimated by a lowered concentration in body fluids or cells, or, more rarely, by the specific appearance during illness of a clinically evident avitaminosis.

CONSERVATION AND REPLACEMENT OF NUTRIENTS.-- The depletion of body nutrients during even a mild, self-limited, short-term infection may take weeks to be restored following clinical recovery from the illness.[3,4] The depletion of nutrients stores is generally most marked shortly after the acute illness has been cured. Stores of lost body nutrients begin to be replaced during convalescence, but they are replenished only gradually. Although the nutritional losses incurred during a brief mild infection are of no great clinical importance, the same cannot be said regarding febrile infections that are severe or protracted. Careful attention to the state of body nutrition during the course of subacute and chronic infections can reduce or even prevent some of the expected depletions.[66] The maintenance during illness of an adequate intake of caloric sources derived from carbohydrate and lipid

nutrients can help to minimize ongoing losses of other body nutrients, especially those involving nitrogenous compounds. If an adequate caloric intake can be maintained, the intake of high quality protein or a balanced amino acid mixture need not be appreciably higher than normal in order to maintain nitrogen balance.[66] However, when attempting to prevent the depletion of body nitrogen stores during serious infections, there seems to be some positive benefit derived from administering nutrient mixtures that are high in their content of branched chain amino acids.[66]

Therapeutic attempts to maintain an adequate intake of essential nutrients and energy sources take on greater importance in acute infectious illnesses of marked severity and long duration. The normally healthy, well nourished individual who develops an easily treated, or short-lived infectious illness will not suffer an appreciable depletion of body nutrients stores. Such brief illnesses do not require unusual efforts to maintain nutrient intakes during their acute course. Following clinical recovery, the body will be able to reaccumulate, over a period of time, all nutrients that were lost.[3] However, if an illness persists, or if a series of complications or secondary infections develop, the total loss of nutrients will become sizeable unless prevented by appropriate nutritional therapy. If nutritional support is neglected in such instances, serious depletions of body nitrogen and stores of other essential nutrients can be anticipated.

## Sequestration or Redistribution of Body Nutrients

The sequestration or redistribution of certain nutrients during infection appears to be a purposeful, physiologically controlled mechanism for assisting in body defenses against invading microorganisms.

IRON -- The most prominent example of such a nutrient redistribution is the sequestration of iron within tissue stores of hemosiderin and ferritin during infectious or inflammatory states. Concomitantly, plasma iron concentrations decline, sometimes to almost nondectable values, especially in pyogenic bacterial infections. The decline in plasma iron and the accumulation of iron in body stores begins within hours after the onset of fever or symptomatic illness. This phenomenon appears to be mediated by an action of Interleukin-1. Iron sequestration then persists until the infectious disease is cured.[16]

If an infectious disease continues into a chronic state, the sequestered iron remains unavailable for use in red blood cell production. This physiological retention of iron in storage sites can lead to the so called "anemia of infection." This form of anemia resembles iron deficiency anemia, in that the red blood cells are hypochronic and microcytic and the plasma iron values are low.[16] However, in infection, adequate or higher than normal amounts of iron can be demonstrated in reticuloendothelial storage sites within the liver, spleen and bone marrow. Further, total iron-binding values in plasma tend to be reduced in infection, whereas plasma ferritin values are high. The depressed iron binding capacity and high ferritin values of infection are the reverse of changes seen in simple iron deficiency anemia.[16]

It is not certain if plasma transport proteins such as transferrin or lactoferrin play a mechanistic role in assisting iron to enter storage depots during infection.[67] It is also controversial as to whether the accumulation of hepatic iron is caused by an accelerated uptake of iron by the liver, or a diminished release of iron from the liver. In any event, the normal flux of iron between plasma and tissue stores is altered so as to allow iron to

accumulate within body storage sites. Iron is not normally lost from the body in excess quantities during most infectious diseases, unless there is overt bleeding or other losses of whole blood.[15]

The sequestration of iron appears to be an important factor in reducing the ability of iron-requiring bacteria to proliferate within body tissues. When iron enters tissue depots during infection, the plasma carrier proteins for iron (i.e., transferrin and lactoferrin) become less saturated.[16] Because the affinity constant of these proteins for binding the iron in plasma is greater than the iron-binding affinity of any bacterial sideophore, the unsaturated transferrin and lactoferrin molecules provide an important mechanism for withholding free iron from its potential availability to bacterial invaders.[16] Many bacteria cannot proliferate if they lack sufficient iron, and they secrete iron-binding siderophores in an attempt to acquire iron from surrounding environments. In this regard, the release of lactoferrin by neutrophils in localized inflammatory lesion provides an additional mechanism for insuring that extracellular iron is bound to a host protein and that its availability is thereby denied for bacterial growth. Concentrations of iron in the proper range are also necessary for some bacteria to produce toxic substances. Because of this, the reduced availability of iron can also serve to protect the body by diminishing bacterial toxin production.

In patients with severe protein malnutrition and a depletion of body nitrogen stores, a reduced ability to synthesize iron-binding plasma proteins can reduce the effectiveness of these proteins as direct antimicrobial factors. In some clinical situations, it has proved dangerous to administer therapeutic iron in large amounts to patients who are severely depleted of

body protein and who have reduced concentrations of transferrin in their plasma.[68] If plasma free iron-binding proteins are diminished, they can easily be saturated by any iron given as nutritional therapy, and iron can thus be made available to bacterial invaders. Severely malnourished patients may harbor dangerous pathogens (such as tuberculosis or brucellosis causing bacteria, or malarial parasites) without manifesting symptomatic illness; if iron is given before protein malnutrition is corrected, these infections may flare up in a dramatic and dangerous manner.[16]

ZINC -- Zinc is another element sequestered in the liver by the action of a purposeful physiologic mechanism induced by infection.[3,7,35] Presumably the sequestration of zinc is also beneficial for host resistance, but evidence for this is less than adequate. Like iron, zinc accumulates within the liver in response to stimulation by Interleukin-1.[7] The accumulation of zinc in storage forms requires an initial de novo synthesis of metallothionein by the hepatocytes.[35] The sequestration phenomenon proceeds, however, with surprising speed, and zinc concentrations in plasma begin to decline within a few hours after the onset of symptoms or fever.[35,50] Because the binding of zinc to alpha-2-macroglobulin in plasma is quite strong, the concentrations of total plasma zinc do not fall proportionately to values as low as those of iron. In fact, reductions of plasma zinc during acute infections rarely fall to below 50% of normal.[3,7]

COPPER -- Another example of the physiologic redistribution of body minerals is the hepatic production and secretion of greater than normal quantities of ceruloplasmin and the copper it contains.[3,10] Ceruloplasmin is one of the acute-phase reactant proteins induced by Interleukin-1, and is produced by the liver. The increase in plasma copper during infection is

somewhat more gradual than the rapid declines in iron and zinc, and because of the relatively long half-life of ceruloplasmin in plasma, copper concentrations decline gradually over a period of time after an acute infection has been cured.[3,10]

PATHOLOGICAL REDISTRIBUTIONS -- In some diseases associated with a dysfunction of cellular metabolic processes, excess quantities of sodium accumulate within body cells. Intracellular sodium can not be returned in a normal manner to the extracellular fluids, apparently because the functional capacity is impaired in the sodium pumping mechanisms of external cellular membranes. Accumulation of sodium within cells should be regarded as an example of a pathologic redistribution of a body element rather than a purposeful physiologic mechanism destined to help with host survival.[3]

Since the liver plays a prominent role in the sequestration and redistribution of trace elements during infection, it is not surprising that these processes may be disrupted during diseases such as hepatitis which causes functional failure in molecular mechanisms of hepatocytes. During the second week of acute hepatitis, plasma iron can become abnormally elevated, apparently because the liver fails to retain its stores of iron.[3,16] During hepatitis, there are also unexplained changes in the ability of plasma proteins components to bind zinc as macroligands, and excess amounts of zinc-amino acid microligands may be lost via the urine.[3]

## Functional Effects of Malnutrition on Host Defensive Mechanisms

Loss of body nutrients and the depletion of nutrient pools generally results in a diminished capacity of host resistance mechanism to function normally.[1,13,69,70] The depletion of body proteins and amino acid stores

reduces the ability of the body to synthesize new proteins. All body defensive mechanisms are ultimately dependent on an ongoing synthesis of new proteins, but various aspects of host defense are affected to different degrees by protein deficiency.[1,13,70] Protein deficiency, especially if combined with a deficiency in energy yielding substrates, can reduce the ability of the body to maintain the structural integrity of its anatomical barriers that normally prevent the entry of microorganisms into body tissues. Protein deficiencies also contribute to a diminished ability of mucosal and dermal surfaces to produce important secretions that normally contain antimicrobial factors, such as lysozyme, secretory IgA, or the gastric acidity required to inactivate certain bacteria.[1,70] More importantly, protein malnutrition causes an atrophy of body lymphoid tissues such as the thymus, the tonsils, the lymph nodes, and lymphoid follicles throughout the body.[1,13] The greatest atrophy occurs in areas normally occupied by T-lymphocytes, but, in contrast, B-lymphocyte and plasma cell areas are generally preserved.[1,13] These histological changes are in keeping with clinical observations that cell-mediated immune functions are more severely depressed in protein malnutrition than is humoral immunity.[70]

Deficiencies of vitamins are known to reduce the functional capacity of some of the immune system responses.[13,69] This problem is most important with deficiencies of vitamins that are necessary for the replication of cellular DNA.[13] Lack of vitamins that influence nucleic acid metabolism (i.e., vitamin $B_{12}$, $B_6$, A, and folic acid) can reduce the ability of T-lymphocytes to function normally. This impairs the ability of the body to maintain an adequate cell mediated immunity.

Deficiencies of vitamin C are especially important because they impair the functional ability of neutrophils to migrate when stimulated by chemotactic substances.[13,69] In clinical terms, severe vitamin C deficiency states are accompanied by an inability of the body to develop an inflammatory reaction. A lack of vitamin A is important because it reduces the competence of both B- and T-cells of the immune system, and because it interfers with the integrity of body surface structures.[13,69]

A lack of the essential fatty acids impairs the ability of body cells to maintain the a normal composition of their extracellular membranes. This deficiency can have a deleterious effect on cellular functions important in host defenses, especially those of lymphocyte populations.[13,69]

Deficiences of trace elements can have important consequences in terms of host defense. A lack of iron is especially important because many of the mechanisms required by neutrophils to kill ingested organisms are dependent on iron-containing myeloperoxidases.[13,69] Iron deficiency also leads to impaired function of B- and T-cells.

Zinc deficiency has important effects on both immune system competence and on the structural integrity of dermal and mucosal membranes. A lack of zinc can lead to anatomical disruptions of mucosal and epithelial barriers that normally prevent the invasion of pathogenic microorganisms. Zinc is an essential element required for synthesis of cellular nucleic acids, and therefore zinc deficiency is especially deleterious to the T-cells of the lymphoid system which are necessary for maintaining cell mediated immunity.[13,69] Deficiencies of copper, magnesium and selenium can also cause depressed immunocompetence.

Convalescent Period Nutrition

The early convalescent period, immediately after a successful cure of an infectious disease, is nutritionally a highly important but often neglected period in the longitudinal course of an illness.[3] The immediate convalescent period represents a time when the nutritional stores of the body are quantitatively most depleted. Although the typical patient no longer has symptoms of illness and has regained a feeling of well-being, residual nutritional deficiencies at that time make the body quite susceptible to another superimposed infectious disease.

Early convalescence is also a time of unique nutritional opportunity.[3] Any potential danger that might result from the forced feeding of a patient during acute symptomatic illness is no longer a threat. The anorexia of illness is generally replaced during the early convalescent period by the return of a normal appetite, or even by some degree of hyperphagia. This latter phenomena is most commonly seen in children. If highly nutritious foods are fed during this period of increased appetite, children may quickly be able to reestablish their normal nutritional pools, regain their normal rate of growth, or even achieve a catch-up in growth that corrects any infection-induced growth lags.[3] A similar period of increased appetite may also occur in adult patients who have recovered from an infection. From a nutritional point of view, the early convalescent period thus represents a "window of opportunity" that can be utilized to gain a relatively rapid repletion of the key nutrients that are lost during infection.[3] These nutrients can be resupplied during convalescence without the potential danger of complicating the recovery process or upsetting normal host defense mechanisms. However, unless nutrients are supplied in greater than normal

amounts following an illness, the reaccumulation of body nutrient stores may take a protracted period, varying from weeks to months, depending upon the extent of infection-induced depletions.

The nutritional repletion of a person who has been seriously or chronically ill with infection, i.e., one who has endured severe nutritional depletion, is especially important. Nutritional repletion will help to prevent reinfections that could initiate a downhill cycle or spiral of infection, worsening-malnutrition, and repeated reinfections.

The immunodeficiency syndrome produced by malnutrition can generally be reversed with relative ease, and in a short time, if good nutritional support is provided.[2] There is evidence that some functional components of the complex immune system will recover their competence faster than other components during periods of nutritional rehabilitation. Thus, for short periods of time, refeeding may produce less-than-balanced functional interrelationships among various components of the immune system. However, the dangers of a long continued, nutritionally induced, immunodeficiency state are certainly greater than any potential problems that may arise from transient immune systems imbalances during periods of nutritional rehabilition.

One problem of potential clinical concern during nutritional rehabilition, as described earlier, is that of iron overload in a protein depleted patient.[68] Optimal treatment strategy should insure that protein deficiencies are corrected and that plasma transferin concentrations are reestablished before the initiation of parenteral or oral iron therapy.[16] Latent infections should be treated concurrently if they can be recognized, and any re-emerging infection should be considered as an important threat.

Transitions of Infections from Acute to Subacute, Chronic or Terminal Stages

Relatively complete data are available to define the typical pattern of metabolic and nutritional responses to an acute mild infectious disease.[3] Relatively good data are also available concerning the presence of changes in nutritional status and body composition in patients with chronic infectious illnesses and in patients with infectious complications of terminal medical and surgical diseases or malignant states.[9] However, very little is known about the metabolic, hormonal, and nutritional transitions that take place when an acute infection begins to evolve into a subacute or chronic stage, or when an acute infection becomes superimposed upon another severe disease process.

Attempts have been made to categorize and define such transitions using systematic measurements of a variety of hormonal and biochemical laboratory tests, plus physiological measurements of cardiovascular and respiratory functions.[48] Useful categories to define the immediate clinical status of a patient are based upon the concept that the initial, generalized acute-phase metabolic responses associated with acute sepsis, trauma, or both in combination, are physiologically induced and controlled. These generalized responses cause the classification of a patient to change from a normal "R," or reference, state to an abnormal but physiologically regulated "A" state that represents a typical compensated stress response to sepsis or trauma.[48,65]. If the acute infectious process is cured, these generalized "A" state responses abate.

Little is known about the progression of events or the control mechanisms that characterize a transition of a generalized infection to a subacute or chronic disease. However, such a transition is generally associated with a

continuing low grade or intermittant fever, a further gradual wasting of body stores of somatic proteins and fat, the development of an anemia, a diminishing of output of adrenal steroids, and a gradual transformation of body composition to that of a wasted, cachetic state.[2-4] This wasting process is accompanied, as a rule, by the development of immunological dysfunction and anergy, with defects in cell mediated immunity being most profound.[13] Chronically infected individuals may lose their delayed dermal hypersensitivity responsiveness to all of the common antigens to which they had previously been sensitized. The nutritionally wasted, chronically infected individual has a markedly diminished ability to respond to secondary, superimposed infections by generating a fever or an appropriate leukocytosis.[1-4] Such patients may be unable to generate an inflammatory response or a granulomatus reaction in response to localized microorganisms or foreign antigens.

The occurrence of a protracted septic process creates difficult problems in a traumatized patient, or someone with a coexisting medical or surgical illness or malignancy.[9,29-32,37,47,48,64,65] If the nutritional status of the patient cannot be restored in the continued presence of these complex illnesses, physiologically controlled defensive mechanisms and cellular functions are likely to become incompetent. The abilities of modern medical and surgical techniques to prolong the lives of seriously ill patients and the introduction of drugs with antimetabolic or antiimmunological functions have combined to increase the incidence of patients who develop serious malnutrition. Thus, secondary infections with opportunistic organisms are all-to-common problems in our most modern medical centers.

With protracted sepsis and malnutrition, the earlier metabolic, hormonal, and immunological responses are again altered, marking a transition of a patients from the abnormal but physiologically controlled "A" state to a clearly, pathological condition as defined by as "B," "C," or "D" states.[48] The "B" state predominantly represents a progression of illness in which there is a failure of the hyperdynamic cardiovascular response to supply peripheral cellular needs. This failure is manifested by narrowed arteriovenous oxygen differences indicative of reduced oxygen extraction in tissues and by severe metabolic acidosis.[48] In the "C" state, marked septic hypotensive shock, despite increased cardiac output, is complicated by respiratory insufficiency.[47,48,65] Physiological derangements in the respiratory distress syndrome are associated with an inadequate oxygenation of the blood, pulmonary circulation shunting, and retention of carbon dioxide in the "C" state. The "D" state is characterized by a transition of illness to include primary myocardial failure rather than peripheral vascular system dysfunction.

In addition to these pulmonary or cardiovascular complications of severe sepsis and injury, the lack of key nutrients (including oxygen) soon leads to the ultimate functional breakdown of vital intracellular mechanisms. Functional breakdown of biochemical and molecular systems of body cells can become widespread. When many vital organs or tissues are affected, multiple organ system failure ensues.[63,64] The medical and surgical approaches to managing complex problems of this sort are covered in other chapters of this book.

## SUMMARY

The development of acute generalized infectious illnesses and serious inflammatory reactions is accompanied by the occurence of a large number of interrelated host defensive measures. These constitute the generalized acute-phase response to infection, inflammatory states, or complex trauma. These responses include the development of fever and hypermetabolism, the production of a leukocytic response, the accelerated proteolysis of skeletal muscle, the generation of free amino acids from body somatic protein catabolism, the production of a number of hormones, the synthesis by the liver of acute phase reactant proteins and of various intracellular enzymes, the acceleration within the liver of gluconeogenesis and lipogenesis with a relative suppression of ketogenesis, the redistribution and/or sequestration of various trace elments, and, importantly, the stimulation of immune system activity. These components of the acute-phase generalized, nonspecific metabolic response to acute infection are triggered by the release from activated monocytes and tissue macrophages of endogenous mediators which are currently grouped under the term Interleukin-1.

The metabolic, hormonal, and physiological components of the generalized response to infectious diseases are quite uniform from one infection to another. The generalized acute-phase responses appear to have special survival value by stimulating a large variety of nonspecific host defenses as well as by activating the immune system. This latter phenomena increases the functional capacity of lymphocytes to develop cellular and humoral immunity against specific antigens contained within the invading microorganism.

The magnitude of these generalized responses is governed by the severity and duration of illness. However, these generalized acute-phase responses are not without their costs to the body, for they result in a wasting of muscle mass, an increased consumption of body nutrients (especially the amino acids), and they lead to absolute losses from the body of nitrogen and elements normally present inside body cells. The nutritional costs of infection are influenced importantly by the height and duration of fever, and to a lesser degree by the presence of anorexia. Infection-induced depletions of body nutrients serve to weaken host resistance.

Infections that become localized in single organ systems cause additional changes in host metabolism and nutritional losses which are superimposed upon the generalized metabolic responses described in preceeding paragraphs. The complications of some infections can result in major derangements of acid base balance and of salt and water metabolism. If acute infections are not cured rapidly, they may progress to subacute or chronic illnesses accompanied by a severe depletion of body nutrients and an eventual failure of host defensive mechanisms. Severe progressive infections can also lead to functional derangements in the respiratory and cardiovascular systems, hypotensive shock, tissue anoxia, and cardiac failure. The accompanying inability of individual body cells to maintain normal functions can also give rise to multi-organ failure and death.

REFERENCES

1. Beisel WR. Nutrition, infection, specific immune responses, and nonspecific host defenses: A complex interaction. In Watson RR (ed). Nutrition, Disease Resistance, and Immune Function. New York: Marcel Dekker, Inc. 1984:1:3-34. (IN PRESS)

2. Beisel WR. Effects of infection on nutritional status and immunity. Fed Proc 1980; 39:3105-3108.

3. Beisel WR. Metabolic effects of infection. In Chandra RK (ed). Progress in Food and Nutrition Science. New York: Pergamon Press, 1984. (IN PRESS)

4. Beisel WR. Magnitude of the host nutritional responses to infection. Am J Clin Nutr 1977; 30:1236-1247.

5. Wiles JB, Cerra FB, Siegel JH et al. The systemic septic response: does the organism matter? Crit Care Med 1980; 8:55-60.

6. Beisel WR. Mediators of fever and muscle proteolysis. N Engl J Med 1983; 308:586-588.

7. Beisel WR, Sobocinski PZ: Endogenous mediators of fever-related metabolic and hormonal responses. In Lipton JM (ed). Fever. New York: Raven Press, 1980:39-48.

8. Beisel WR, Wannemacher RW Jr. Gluconeogenesis, ureagenesis, and ketogenesis during sepsis. JPEN 1980; 4:277-285.

9. Cerra FB, Siegel JH, Coleman B et al. Septic autocannibalism. A failure of exogenous nutritional support. Ann Surg 1980; 192:570-580.

10. Powanda MC, Beisel WR. Hypothesis: leukocyte endogenous mediator/endogenous pyrogen/lymphocyte-activating factor modulates the development of nonspecific and specific immunity and affects nutritional status. Am J Clin Nutr 1982; 35:762-768.

11. Beisel WR. Alterations in hormone production and utilization during infection. In Powanda MC, Canonico PG (eds). Infection. The Physiologic and Metabolic Responses of the Host. Amsterdam: Elsevier North-Holland Biomedical Press, 1981:147-172.

12. Dinarello CA. Interleukin-1. Rev Infect Dis, 1984; 6:51-95.

13. Levy JA. II. Nutrition and the immune system. In Stites DP, Stobo JD, Fudenberg HH et al. (eds). Basic and Clinical Immunology. 4th ed. Los Altos, California: Lange Medical Publications, 1982:297-305.

14. Bornstein DL. Leukocyte pyrogen: A major mediator of the acute phase reaction. Ann NY Acad Sci 1982; 389:323-337.

15. Beisel WR, Wannemacher RW Jr, Neufeld HA. Relation of fever to energy expenditure. In Kinney JM (ed). Assessment of Energy Metabolism in Health and Disease. Columbus, Ohio: Ross Laboratories, 1980:144-150.

16. Beisel WR. Iron nutrition: Immunity and infection. Resident and Staff Physician 1981; 37-42.

17. Clowes, GHA Jr, George BC, Villee CA Jr et al. Muscle proteolysis induced by a circulating peptide in patients with sepsis or trauma. N Engl J Med 1983; 308:545-552.

18. Baracos V, Rodemann HP, Dinarello CA et al. Stimulation of muscle protein degradation and prostaglandin $E_2$ release by leukocytic pyrogen (interleukin-1). A mechanism for the increased degradation of muscle proteins during fever. N Engl J Med 1983; 308:553-558.

19. Astrom E, Friman G, Pilstrom L. Human skeletal muscle in bacterial infection: Enzyme activities and their relationship to age. Scand J Infect Dis 1977; 9:193-195.

20. Ilback N-G. Striated muscle in infection. Uni of Uppsala, 1983; Thesis 686:1-49, University of Uppsala, Sweden.

21. Powanda MC, Dinterman RE, Wannemacher RW Jr et al. Tryptophan metabolism in relation to amino acid alterations during typhoid fever. Acta Vitaminol Enzymol (Milano) 1975; 29:164-168.

22. O'Donnell TF Jr, Clowes GHA Jr, Blackburn GL et al. Proteolysis associated with a deficit of peripheral energy fuel substrates in septic man. Surgery 1976; 80:192-200.

23. Mosher DF. Changes in plasma cold-insoluble globulin concentration during experimental Rocky Mountain spotted fever infection in rhesus monkeys. Throm Res 1976; 9:37-45.

24. Fearon DT, Ruddy S, Schur PH et al. Activation of the properdin pathway of complement in patients with gram-negative bacteremia. N Engl J Med 1975; 292:937-940.

25. Fine D, Mosher D, Yamada T et al. Coagulation and complement studies in Rocky Mountain spotted fever. Arch Intern Med 1978; 138:735-738.

26. Wing DA, Yamada T, Hawley HB et al. Model for disseminated intravascular coagulation: bacterial sepsis in rhesus monkeys. J Lab Clin Med 1978; 92:239-251.

27. Mason JW, Kleeberg U, Dolan P et al. Plasma kallikrein and Hageman factor in gram-negative bacteremia. Ann Intern Med 1970; 73:545-551.

28. Satterwhite TK, Hawiger J, Burklow SL et al. Degradation products of fibrinogen and fibrin in bacteremia due to gram-negative rods. J Infect Dis 1973; 127:437-441.

29. Askanazi J, Carpentier YA, Michelsen CB et al. Muscle and plasma amino acids following injury. Influence of intercurrent infection. Ann Surg 1980; 192:78-85.

30. Freund HR, Ryan JA Jr, Fischer JE. Amino acid derangements in patients with sepsis: Treatment with branched chain amino acid rich infusions. Ann Surg 1978; 188:423-430.

31. Marchuk JB, Finley RJ, Groves AC et al. Catabolic hormones and substrate patterns in septic patients. J Surg Res 1977; 23:177-182.

32. Cerra FB, Caprioli J, Siegel JH et al. Proline metabolism in sepsis, cirrhosis and general surgery. Ann Surg 1979; 190:577-586.

33. Little JS. Synthesis, transport, and secretion of plasma proteins by the livers of control and Streptococcus pneumoniae-infected rats. Infect Immun 1978; 22:585-596.

34. Thompson WL, Wannemacher RW Jr. Effects of infection and endotoxin on rat hepatic RNA production and distribution. Am J Physiol 1980; 238:G303-G311.

35. Sobocinski PZ, Canterbury WJ Jr, Mapes CA et al. Involvement of hepatic metallothioneins in hypozincemia associated with bacterial infection. Am J Physiol 1978; 234:E399-E406.

36. Long CL, Kinney JM, Geiger JS. Nonsuppressibility of gluconeogenesis by glucose in septic patients. Metabolism 1976; 25:193-201.

37. Cerra FB, Siegel JH, Border JR et al. The hepatic failure of sepsis: Cellular versus substrate. Surgery 1979; 86:409-422

38. Nolan JP. The role of endotoxin in liver injury. Gastroenterology 1975; 69:1346-1356.

39. McCallum RE, Seale TW, Stith RD. Influence of endotoxin treatment on dexamethasone induction of hepatic phosphoenolpyruvate carboxykinase. Infect Immun 1983; 39:213-219.

40. Wilmore DW, Long JM, Mason AD Jr et al. Mediator of the hypermetabolic response to thermal injury. Ann Surg 1974; 180:653-699.

41. Carpentier YA, Askanazi J, Elwyn DH et al. Effects of hypercaloric glucose infusion on lipid metabolism in injury and sepsis. J Trauma 1979; 19:649-654.

42. Beisel WR, Fiser RH Jr. Lipid metabolism during infectious illness. Am J Clin Nutr 1970; 23:1069-1079.

43. Neufeld HA, Pace JG, Kaminski MV et al. A probable endocrine basis for the depression of ketone bodies during infectious or inflammatory state in rats. Endocrinology 1980; 107:596-601.

44. Kaufmann RL, Matson CF, Rowberg AH et al. Defective lipid disposal mechanisms during bacterial infection in rhesus monkeys. Metabolism 1976; 25:615-624.

45. Scrimshaw NS, Taylor CE, Gordon JE. Interactions of nutrition and infection. WHO Monograph Series 1968; 57:148-166.

46. Watten RH, Morgan FM, Songkhla YN et al. Water and electrolyte studies in cholera. J Clin Invest 1959; 38:1879-1889.

47. Clowes GHA Jr, Hirsch E, Williams L et al. Septic lung and shock lung in man. Ann Surg 1975; 181:681-692.

48. Siegel JH, Giovannini I, Coleman B. Ventilation:perfusion maldistribution secondary to the hyperdynamic cardiovascular state as the major cause of increased pulmonary shunting in human sepsis. J Trauma 1979; 19:432-460.

49. Chang GT, Moulder JW. Loss of inorganic ions from host cells infected with Chlamydia psittaci. Infect Immun 1978; 19:827-832.

50. Cousins RJ. Relationship of metallothionein synthesis and degradation to intracellular zinc metabolism. Dev Toxicol Environ Sci 1982; 9:251-262.

51. Rupp RG, Fuller GM. The effects of leucocytic and serum factors on fibrinogen biosynthesis in cultured hepatocytes. Exp Cell Res 1979; 118:23-30.

52. Schlick E, Hartung K, Piccoli M et al. The capacity of biological response modifiers (BRM) to induce the secretion of colony stimulating factor(s) by murine macrophages and human monocytes. Fed Proc 1983; 42:1221.

53. Mizel SB, Dayer J-M, Krane SM et al. Stimulation of rheumatoid synovial cell collagenase and prostaglandin production by partially purified lymphocyte-activating factor (interleukin-1). Proc Natl Acad Sci 1981; 78:2474-2477.

54. Filkins JP, Yelich MR. Mechanism of hyperinsulinemia after reticuloendothelial system phagocytosis. Am J Physiol 1982; 242:E115-E120.

55. Thompson WL, Abeles FB, Beall FA et al. Influence of the adrenal glucocorticoids on the stimulation of synthesis of hepatic ribonucleic acid and plasma acute-phase globulins by leucocytic endogenous mediator. Biochem J 1976; 156:25-32.

56. Wannemacher RW Jr, Pekarek RS, Klainer AS et al. Detection of a leukocytic endogenous mediator-like mediator of serum amino acid and zinc depression during infectious illnesses. Infect Immun 1975; 11:873-885.

57. Zipser RD, Davenport MW, Martin KL et al. Hyperreninemic hypoaldosteronism in the critically ill: A new entity. J Clin Endocrinol Metab 1981; 53:867-873.

58. Gruchow HW. Catecholamine activity and infectious disease episodes. J Human Stress 1979; 5:11-17.

59. Buescher EL, Belfer ML, Artenstein MS et al. A prospective study of corticosteroid and catecholamine levels in relation to viral respiratory illness. J Human Stress 1979; 5:13-23.

60. Wartofsky L. The response of the thyroid gland and thyroid hormone metabolism to infectious disease. Horm Res 1974; 5:112-128.

61. Cahill GF Jr. Starvation in man. Clin Endocrinol Metab 1976; 5:397-415.

62. Lewis T. Inflammation as a disease mechanism. In Sweifach BJ, Grant L, McCluskey RT (eds). The Inflammatory Process III. 2nd ed. New York: Academic Press, 1974:515-518.

63. Bell RC, Coalson JJ, Smith JD et al. Multiple organ system failure and infection in adult respiratory distress syndrome. Ann Intern Med 1983; 99:293-298.

64. Border JR, Chenier R, McMenamy RH et al. Multiple systems organ failure: Muscle fuel deficit with visceral protein malnutrition. Surg Clin of North Am 1976; 56:1147-1167.

65. Siegel JH, Cerra FB, Coleman B et al. Physiological and metabolic correlations in human sepsis. Surgery 1979; 86:163-193.

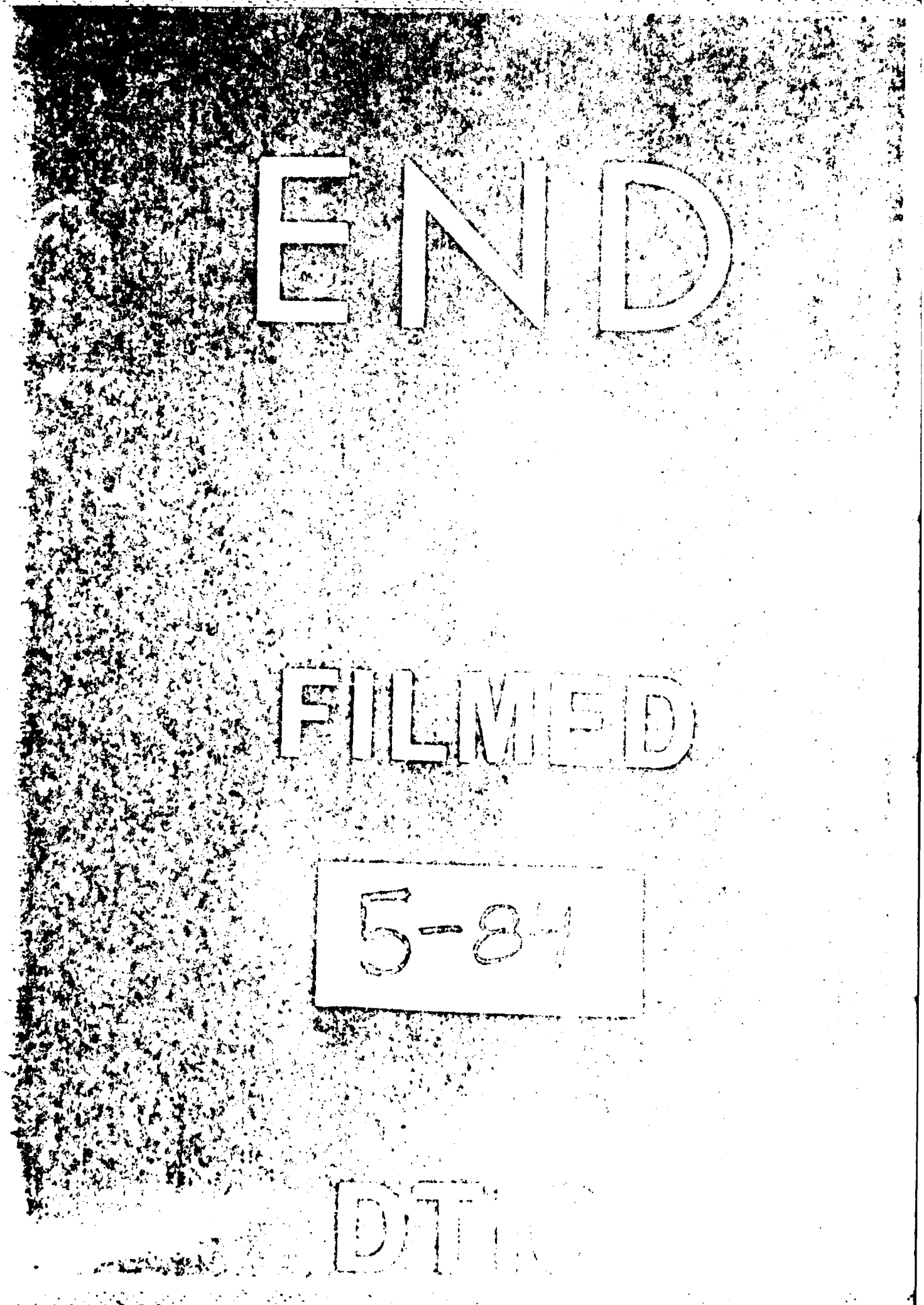
66. Wannemacher RW Jr, Kaminski MV Jr, Neufeld HA. Protein-sparing therapy during pneumococcal infection in rhesus monkeys. JPEN 1978; 2:507-518.

67. Van Snick JL, Masson PL, Heremans JF. The involvement of lactoferrin in the hyposideremia of acute inflammation. J Exp Med 1974; 1068-1084.

68. Murray MJ, Murray AB. Starvation suppression and refeeding activation of infection. An ecological necessity? Lancet 1977; 1:123-125.

69. Beisel WR. Single nutrients and immunity. Am J Clin Nutr 1982; 35:415-468.

70. Chandra RK, Newberne PM. Nutrition, Immunity, and Infection. New York: Plenum Press, 1977:1-246.


END
FILMED
5-84
DTIC